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THE CAUSE OF SO-CALLED IDIOPATHIC HYDROCEPHALUS

By WALTER E. DANDY

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Until recently all cases of hydrocephalus were considered idiopathic. We think it is now fair to assume that those cases in which an obstruction in the ventricular system can be demonstrated may be liberated from this *terra incognita* and may now be classified according to an established pathology; for there can no longer be any doubt concerning the cause of obstructive hydrocephalus. Any lesion which occludes the ventricular system will always produce stasis of fluid and dilatation of the ventricles proximal to the obstruction but will not change the size of the ventricles distal to it. There can be no exception to this rule. The proof of this causative relationship has been amply provided in recent necropsy material[1] and in the experimental production of the disease at will.[2, 3, 4, 5]

The purpose of this paper is to present proof—which I believe is just as positive—of the cause of the remaining big group of this disease—*communicating hydrocephalus, i. e.*, of that type of hydrocephalus in which all the ventricles are in communication with the subarachnoid space. In the course of intensive studies on the absorption of cerebrospinal fluid in hydrocephalus it was found that in the communicating type the absorption from the subarachnoid space was greatly reduced. A reduction in the amount of the absorbing spaces which are reached by the cerebrospinal fluid was suspected as the cause and a hypothetical pathology suggested along this line of reasoning.[1] Later, four cases of communicating hydrocephalus were studied at necropsy and in each adhesions were found which obliterated the cisternæ; hence it was assumed that, by preventing the cerebrospinal fluid from reaching the great absorbing spaces over the cerebral hemispheres, these adhesions had caused the hydrocephalus.[2] We realized, however, the necessity of a more graphic demonstration of the lesion and of proof of its effects before these findings could be accepted beyond question.

[1] Dandy, W. E., and Blackfan, K. D.: Internal Hydrocephalus—an Experimental, Clinical and Pathological Study. J. A. M. A., 1913, lxi, 2216; Am. J. Dis. Child., 1914, viii, 406.

[2] Dandy, W. E.: Experimental Hydrocephalus. Ann. Surg., August, 1919, p. 129.

[3] Weed, L. H.: The Experimental Production of an Internal Hydrocephalus. Publication 272, Carnegie Institute of Washington, p. 425.

[4] Thomas, W. T.: Experimental Hydrocephalus. J. Exper. Med., 1914, xix, 106.

[2] Dandy, W. E., and Blackfan, K. D.: Internal Hydrocephalus. Second paper. Am. J. Dis. Child., 1917, xiv, 424.

There are two ways in which an obstruction of the cisternæ can be clearly shown—one after death, the other in the living patient. (1) If a colored suspension is carefully injected into the spinal canal before making an autopsy[5] the color will reach but cannot pass an obstruction in the cisternæ. (2) If air is injected into the spinal canal of a living patient, the roentgenogram will show the air extending up to but not beyond the point of obstruction in the cisternæ.[6, 7] Unless these tests are positive, an obstruction in the cisternæ or elsewhere cannot be presumed to exist nor considered to be the cause of communicating hydrocephalus. If properly applied, either test will prove conclusively that an obstruction either is or is not present.

A third and equally important proof must be forthcoming before the cause of communicating hydrocephalus can be regarded as solved: it must be shown that a lesion similar to the one described in these cases of communicating hydrocephalus and similarly situated will cause hydrocephalus when experimentally produced in animals.

Communicating Hydrocephalus Experimentally Produced

In the studies presented here, all of these exactions have been met. First I have produced communicating hydrocephalus in dogs by making a barrier of adhesions in the mesencephalic cisterna[8] (Fig. 1). Shortly before necropsy on these animals a suspension of India ink was substituted for an equal amount of cerebrospinal fluid which had been aspirated from the cisterna magna through a puncture of the occipito-atlantal membrane. When India ink is introduced into the spinal canal of an animal whose cerebrospinal spaces are intact, the color will find its way within two hours to every point of the subarachnoid space over both cerebral hemispheres. But in the experimental animal with the perimesencephalic band of adhesions, the passage of the ink is abruptly terminated by the obstructing band and none of the color reaches the surface of either cerebral hemisphere (Figs. 3, 4); furthermore, as a result of the hydrocephalus which has developed, the foramina of Luschka and Magendie have become so dilated that a retrograde flow of ink is freely permitted into all the cerebral ventricles (Fig. 3). The entrance of ink into the furthermost recesses of the ventricles (which normally occurs only at times) shows that the color has had every opportunity to reach the cerebral sulci, but is precluded from doing so by the obstruction.

Demonstration of Obstruction in the Subarachnoid Space at Post-Mortem Examination

Knowing from the experiments that an obstruction in the cisterna produces communicating hydrocephalus, it then remains to prove that all or at least many cases of this disease have this as the causative lesion. The graphic color method should be applied to all human necropsy material in which hydrocephalus is suspected or known to be present. It is important that pressure be avoided in introducing these colored solutions, for delicate adhesions, though sufficient to cause an obstruction during life, may be easily ruptured and in this way artificial results may be obtained. In animals, the color can be introduced without pressure during life and the normal circulation will convey the fluid to all the spaces which are patent. In necropsy material the results, though less perfect, will be satisfactory if the color is introduced by gravity for 15 or 20 minutes.

Despite studies in a large series of cases of hydrocephalus, we have had but one opportunity of applying this method at a post-mortem examination in a case of hydrocephalus with communication. In this instance the results were just as striking as in the experimental cases which have been described; the color filled the cisternæ, even the cisterna interpeduncularis, covered the cerebellar subarachnoid spaces, but failed to reach any of the sulci over either cerebral hemisphere (Figs. 17, 18, 19). On the other hand, the ink passed freely into every part of the cerebral ventricles, deeply staining their walls (Fig. 18), for both foramina of Luschka and the foramen of Magendie were widely open (Fig. 19). No gross adhesions could be seen either in the vicinity of these openings or even along the cisternæ; nevertheless, the cerebral sulci could not be reached by the colored solution, because the branches issuing from the cisternæ were sealed. The character of the pathological lesion will be discussed later; the test demonstrates that an obstruction exists in the cisternæ and with the additional support of the experimental evidence no doubt can exist that this obstruction is the cause of the hydrocephalus.

Why Should an Obstruction in the Cisternæ Cause Hydrocephalus?

Doubtless obstructions, similar to those which we are about to describe in communicating hydrocephalus, have been present in all necropsies of this disease. The adhesions may not be striking, and at times could be missed entirely, if one did not look for them. Indeed in some cases the lesion may be due to defective formation of the cerebrospinal spaces in the early embryo. These pathological findings become significant and all-important only when the anatomy of the cerebrospinal spaces and the manner and place of the formation and the absorption of cerebrospinal fluid are fully understood.

Cerebrospinal fluid circulates in a mesothelial-lined vascular system which is just as definite as the vascular systems for blood, lymph or bile. A clear conception of the gross plan of this vascular system can be obtained from the accompanying diagram by Max Brödel (Fig. 5). The cavities in the interior of the brain (the ventricular system) are concerned only with the *production* of cerebrospinal fluid; the spaces on the exterior of the brain (the subarachnoid spaces) are normally concerned only with the *absorption* of cerebrospinal fluid. The balance between the production and absorption of fluid is maintained by three closely grouped communicating open-

[6] Dandy, W. E.: Roentgenography of the brain after the injection of air into the spinal canal. Ann. Surg., October, 1919, p. 397.

[7] Dandy, W. E.: Ventriculography following the injection of air into the cerebral ventricles. Ann. Surg., July, 1918, p. 5.

ings—the foramina of Luschka and that of Magendie (Fig. 19). Only through these openings can fluid escape from the entire ventricular system; consequently, closure of these openings always produces a stasis of fluid—hydrocephalus—in all the ventricles. But in communicating hydrocephalus, these conduits are open, either entirely or in part, depending upon the extent and position of the pathological lesion. This type of hydrocephalus is caused by interference with the absorption of the cerebrospinal fluid in the subarachnoid spaces. The real absorbing area of the subarachnoid space is the great network of subarachnoid spaces over the cerebral hemispheres—the cerebral sulci. Here the cerebrospinal fluid is distributed over a very extensive surface of blood capillaries of the pia and passes directly through the capillary walls into the blood by osmosis. Numerous large branches convey the fluid to these spaces from the cisterna chiasmatis and the cisterna interpeduncularis, which together serve as a distributing center for all the cerebrospinal fluid which is destined to reach the cerebral hemisphere. Since all the ventricular fluid, on leaving the ventricles, first reaches the cisterna magna (by way of the foramina of Luschka and Magendie), a relatively long passageway under the medulla, pons, and mid-brain must be traversed before this fluid can reach the cisterna interpeduncularis and the cisterna chiasmatis, whence it can be distributed to the cerebral sulci by the major branches, as described (Fig. 5). The finer anatomy and histology of these spaces have been well described by Weed.[5, 8]

By experimental methods, which have been mentioned in earlier publications, it has been shown that from three-fourths to four-fifths of the cerebrospinal fluid is absorbed from the subarachnoid spaces of the brain, and the remaining one-quarter or one-fifth in the spinal subarachnoid space. It is doubtful if any absorption occurs in the cisternæ, these channels probably serving only as large conduits to carry the fluid to the surface of the brain, much as the ureters carry the urinary secretion to the bladder. An obstruction in the cisternæ under the medulla, pons or mesencephalon (that is, at any point between the foramina of Luschka and the cisterna interpeduncularis) will produce a stasis of fluid up to the point of obstruction and cause hydrocephalus just as effectively as would a block at the aqueduct of Sylvius or at the foramina of Luschka and Magendie. It will be remembered that through the membranous tentorium cerebelli which separates the posterior and middle cranial cavities there is but one opening, and this is only a little larger than the brain stem (mesencephalon) which passes through it. It is evident that when adhesions close the incisura tentorii and obliterate the mesencephalic cisterna, collateral channels for the distribution of cerebrospinal fluid have no possible way to develop.

[5] Weed, L. H.: An Anatomical Consideration of the Cerebrospinal Fluid. Anat. Record, 1917, xii, p. 461.

[8] Weed, L. H.: Cells of the Arachnoid. Bull. Johns Hopkins Hosp., 1920, xxxi, p. 343.

Intra Vitam Method of Demonstrating an Obstruction in the Subarachnoid Space

The value of intraspinous injections of air will be apparent when it is realized that every part of the subarachnoid space can be reproduced [6] in the roentgenogram, just as every part of the ventricular system can be reproduced by an *intraventricular* injection of air.[7] At times, the ventricles also can be injected from the spinal puncture and, again, the subarachnoid space may be partially or wholly injected by way of the ventricular puncture. The patient is placed in the recumbent position, with the head exactly horizontal and higher than the body. This position must be carefully maintained until the skiagram has been taken. In the normal adult, about 30 to 60 c. c. of fluid can be obtained by lumbar puncture and an equal quantity of air, which is substituted, will fill all parts of the subarachnoid space. The cerebral sulci are shown as a network of lines over the brain (Fig. 6). The presence or absence of these air-filled sulci is the crucial observation of all intraspinous injections. Normally, the sulci will always be filled. When they can be seen over the entire cerebral hemisphere, it is evident that every part of the subarachnoid space is patent. Intact subarachnoid spaces may be interpreted to mean that hydrocephalus, if present, cannot be of the communicating type; if, therefore, hydrocephalus is present (with air-filled sulci) an obstruction must be located in the ventricular system. On the other hand, the absence of air in the cerebral sulci means that an obstruction exists in some part of the subarachnoid space; it also indicates that hydrocephalus must exist because the cerebrospinal fluid (air) cannot reach the absorbing spaces of the cerebral hemispheres; the hydrocephalus with such pneumographic findings would be of the communicating type or possibly of an obstructive type, which, if corrected, would only be transformed into a communicating type.[6, 7]

When intact, the cisternal conduit can often be seen throughout the entire course, even through the dense petrous portion of the temporal bone; the major branches can frequently be seen passing directly from the cisterna chiasmatis and the cisterna interpeduncularis to the cerebral sulci; and when an obstruction exists at any point along the cisternæ, it is located definitely by the furthermost point of the air shadow. The cisterna magna is usually clearly outlined. A marked variation has been found in its size; to a certain extent, I believe its size depends upon effects of adhesions, which are so frequently present; for if the cerebellar lobes are firmly bound to the dura in the neighborhood of the foramen magnum, it is clear that the size of the cisterna magna will be reduced and that its enlargement which would otherwise naturally occur with hydrocephalus will be impossible. In obstructive hydrocephalus the size of the cisterna magna is usually reduced by the backward pressure of the superimposed dilated ventricles, the contents of which have no avenue of escape into the cisternæ.

[6, 7] Dandy, W. E.: *Loc. cit.*

Location of Occlusions of the Subarachnoid Space

Obviously an obstruction can exist at any part of the subarachnoid tree and the results, in terms of hydrocephalus, will be dependent upon the location of the obstruction. The obstruction may be in the trunk of the tree (the cisternæ); it may occlude all the main branches which carry fluid from the cisternæ to the cerebral sulci; it may occlude some, but not all, of these branches; or finally, more or less extensive local areas of the subarachnoid space may be obliterated. An obliteration of the cisternæ or of all the distributing branches will prevent any cerebrospinal fluid from reaching any of the cerebral sulci; occlusion of some but not all the branches of the cisternæ may or may not produce hydrocephalus according to the number of cerebral sulci which continue to receive fluid through the branches which remain intact; or a low grade of hydrocephalus may develop because part of the fluid will be handled by the patent sulci. Extensive local areas of the cerebral subarachnoid space may be destroyed without the occurrence of any hydrocephalus, because the normal subarachnoid spaces are far in excess of the normal requirement for absorption; this is demonstrated by the results of every cranial operation, following which adhesions obliterate extensive areas of subarachnoid spaces with no effect upon the balance of cerebrospinal fluid.

Obstruction in the Cisternæ

The most frequent location for an obstruction in communicating hydrocephalus is in the cisternæ. This was first observed in the four cases which were carefully studied at necropsy and will be seen in the results which are to follow in the patients who have been studied by cerebral pneumography. One must not infer from this statement that adhesions only in the cisternæ exist in these cases, but merely that these are the adhesions which are directly responsible for the production of the hydrocephalus. As a matter of fact, there are frequently more or less extensive adhesions along the entire base of the brain, particularly over both cerebellar lobes, and even over the cerebral hemispheres. Frequently one or two of the three basal foramina (Luschka and Magendie) may be sealed by these adhesions (Fig. 12) and at times the lumen of the third opening may be implicated. When all three openings are occluded, obstructive hydrocephalus results; when one or more foramina are patent, the hydrocephalus is of the communicating type.

Certainly the vast majority of all cases of communicating hydrocephalus follow meningitis (Fig. 8) and, being a post-meningitic process, the obstruction of the cisternæ is in keeping with the basilar involvement of most forms of meningitis. It is also worthy of note that the great majority of these cases occur in infants and young children in whom meningitis is so prevalent and in whom the delicate meninges are more susceptible to permanent injury. At times the meningitic process may be of prenatal origin. This is shown by the frequent occurrence of this type of hydrocephalus at birth and by the presence of the basilar adhesions as the etiological factor; also by the coexistence of a meningocele which is doubtless caused by the same general process.

In more than half of our cases of communicating hydrocephalus the disease has definitely arisen at some time after birth, usually following an illness which has been variously diagnosed, but which a careful history will prove to have been meningitis. Again, the hydrocephalus has almost certainly followed an acute illness, perhaps even very mild, but which on the most careful inquiry has yielded none of the signs or symptoms of meningitis. In these cases adhesions have been found, either at necropsy or at operation, denoting that this illness must have been meningitis. At other times, though quite rarely, it is even possible to find at the base of the brain and elsewhere adhesions which could have been caused only by a pre-existing meningitis, although no illness may have been observed by the parents. These facts show the importance of a careful history of all patients suffering from intracranial pressure; they show that characteristic full-blown signs and symptoms of meningitis are not always present; and that the post-meningitic adhesions are not necessarily in proportion to the severity of the attack of meningitis. The situation, not the extent, of the post-meningitic adhesions determines the onset and severity of the resulting hydrocephalus. Communicating hydrocephalus can, of course, result from obstruction of the cisternæ by tumors of the pons and mid-brain and even by tumors situated in the middle cranial fossa; instances of these relationships have been reported in previous papers.[9, 10] The effects on the circulation of the cerebrospinal fluid are exactly the same whether the occlusion of the subarachnoid space is caused by tumor or by adhesions; but because of differences in treatment, the consideration of occlusions by neoplasms will not be considered here.

In seven out of ten patients with communicating hydrocephalus studied by cerebral pneumography, the obstruction has been located in the pontine or mesencephalic cisterna. In each of these, the column of air ended abruptly under the pons or mid-brain and no air reached the cerebral sulci; in each, the air passed freely into the lateral ventricles, demonstrating the free communication between the ventricles and the spinal subarachnoid space; in each, the cisterna magna was also seen, but its size varied greatly. In one instance it was scarcely visible, doubtless because adhesions between the cerebellum and the adjacent dura had obliterated this usually large chamber of fluid. In other instances the cisterna magna was greatly enlarged—even to the same degree as the fourth ventricle (Figs 9, 10). The pontine and mesencephalic cisternæ showed some variation in size.

Several times, when performing cerebellar operations on patients with hydrocephalus, I have been impressed with the fact that the cisterna magna, which usually covers nearly one-half of the posterior surface of both cerebellar lobes, was very small and at times were scarcely recognizable. Invariably in

[9] Dandy, W. E.: *Loc. cit.*

[10] Dandy, W. E.: Localization or Elimination of Cerebral Tumors by Ventriculography. Surg., Gynec. and Obst. April, 1920, p. 329.

these cases the cerebellum was tightly bound to the dura by adhesions. These operative findings, together with the necropsy observations, explain the cause of the pneumographic variation in the size of the cisternæ.

It has, doubtless, occurred to many, as to ourselves, to ask why hydrocephalus should be *internal* when the fluid can pass from the ventricles to the exterior. The fact that the cerebrospinal fluid forms in the ventricles and that the fluid is dammed back to its source only partially answers this question. The full answer is now clear. When an obstruction exists in the mesencephalic or pontine cisternæ, the extraventricular distribution of cerebrospinal fluid is restricted to the subarachnoid spaces in the posterior cranial fossa, and usually these spaces are reduced to less than normal size by the post-inflammatory process. The cisterna magna will be proportionately as large as the fourth ventricle when its enlargement is not precluded by adhesions; in other words the accumulation of cerebrospinal fluid and the dilatation of the fluid-containing spaces will occur up to the obstruction (the causative lesion) and the size of the various collections of fluid in these spaces will be dependent on the resistance offered.

Occlusion of All the Main Branches of the Cisterna Interpeduncularis and the Cisterna Chiasmatis

In two of our cases the occlusion was not in the cisternæ but in the large branches which radiate from the cisternæ interpeduncularis and chiasmatica and which carry the cerebrospinal fluid to all the surfaces of the cerebral hemispheres. Although the anatomical features of the two cases differed greatly, fundamentally they were similar in that the cisternæ were patent but all the branches were sealed. In each case the clinical diagnosis of communicating hydrocephalus was established by the phenolsulphonephthalein test. In each the site of the obstruction was determined by cerebral pneumography. In one case the findings were verified by necropsy and the intraspinal color test; and in the other by operation and the clinical tests. There was nothing unusual in the history of either case, the disease having been noticed soon after birth and having progressed with the usual rapidity until a tremendously large head had resulted. In one a partial fluid balance eventually had been established, as frequently happens, and at the age of four the fontanelles had slowly closed. The other child was only eight months old and the rate of growth of the head had not diminished.

After the injection of air into the younger child, the roentgenogram showed the air to have stopped in the cisterna immediately behind the sella turcica, *i. e.*, at the cisterna interpeduncularis. Only a small amount of air had been injected into the spine, and this passed freely into the lateral ventricles, but not a trace could be found in the cerebral sulci, which normally should fill with greater ease than the ventricles. The cisterna magna and the cisternæ under the brain-stem were small. At necropsy the spinal canal was injected with India ink. The distribution of this color was exactly that of the air as shown by the roentgenogram. The ink did not extend beyond the cisternæ although it reached the region of the optic chiasm. On the other hand, all the recesses of the cerebral ventricles, as well as the entire subarachnoid space surrounding the cerebellum, were filled with the black suspension, showing that the ink had had ample opportunity to reach the cerebral sulci, but had been prevented from doing so by an obstruction. No adhesions were evident during removal of the brain, nor could any be found later on careful inspection of the brain. In all of our other cases of communicating hydrocephalus, adhesions had been found at necropsy and one or two of the basal foramina (Luschka and Magendie) had been included in these adhesions and their closure had resulted. But in this case the foramina of Luschka and that of Magendie were open and larger than normal. In the accompanying photograph (Fig. 19), a wire has been inserted into the three foramina to show their position and condition. The patency or closure of each of these foramina can always be demonstrated easily and absolutely if the probe is passed from the fourth ventricle outward along the lateral recess. The personal equation cannot enter into the determination.

But in the absence of any demonstrable adhesions, and in the presence of an intact cisternal conduit, why do not the cerebral sulci fill? We know that they cannot fill, because both the air before death and the ink after death have been unable to reach them, and by the two tests, either of which should be absolute, an obstructing lesion has been located in identically the same position. There can be only one explanation for the failure of fluid to reach the cerebral sulci, namely, the absence of the main branches which carry the fluid from the cisternæ to the cerebral hemispheres. These branches may be absent either because they have been obliterated by adhesions following meningitis or they may have failed to develop. The absence of adhesion leads me to suspect the latter to be the cause, though the proof is lacking. Weed [8] has shown the cerebrospinal spaces to be a secondary splitting of the peri-encephalic mesenchyme and their development to follow closely upon the opening of the basal foramina, which result from a gradual thinning of the walls of the fourth ventricle; prior to this time the ventricular system is closed. At times these foramina fail to develop [9] and hydrocephalus results, and doubtless the same agenesis, perhaps easier to understand, may account for the failure either of the cisternæ or of its branches to develop.

It is worthy of note that in this case the cisterna is small, whereas it should be larger owing to the accumulated fluid up to the obstruction. The absence of this expected enlargement must indicate a rigid wall, which might be of inflammatory origin or it might be the congenital impediment which prevented the further development of the cisternæ in fœtal life.

In the second case the pathological features at first glance will appear to show little in common with the preceding case. The pathology was disclosed by operation and not by necropsy, but as there was ample opportunity to observe the entire surface of the brain, excepting most of that in the poste-

[9] Dandy, W. E.: The Diagnosis and Treatment of Hydrocephalus resulting from the closure of the foramina of Luschka and Magendie. Surg., Gynec. and Obst., February, 1921.

rior cranial fossa, a post-mortem examination would be of little additional value. Air was injected into a lateral ventricle and not into the spinal canal. As mentioned above, the phenolsulphonephthalein test showed a communicating hydrocephalus. At two operations both hemispheres were explored, and over neither was cerebrospinal fluid found in the cerebral sulci. A huge cyst filled the base of the cranial chamber and extending upward pushed the brain away from the floor of the skull. The cyst extended from one side of the skull to the other, and on each side it was continuous with the cisternæ chiasmatica and interpeduncularis. In fact, on each side it was a direct extension of these cisternæ. Moreover, when the cyst was opened (on either side) the brain-stem could be seen as far as the pons, owing to the tremendous size of the cisternæ under the mid-brain and pons; and doubtless the medullary cisterna was of corresponding size. The chemical analysis of this vast accumulation of fluid showed it to be the same as the cerebrospinal fluid in the lateral ventricles. Furthermore, the phenolsulphonephthalein test demonstrated communication between the ventricles and these extra-cerebral cysts, but only after half an hour. In other words, the communication was by a devious path and was not direct. The absence of air in the cysts after ventricular injection also eliminates any direct communication, and finally, at operation there was seen to be no direct communication.[12]

We are dealing, therefore, with a case of communicating hydrocephalus in which the obstruction is at the branches which pass from the cisterna interpeduncularis and the c. chiasmatis to the surfaces of the cerebral hemispheres (there being no fluid in the cerebral sulci). The walls of the cisternæ, gradually yielding to the pressure of the accumulating fluid, allow the formation of the huge cysts instead of the usually restricted cisterna under the brain. No adhesions of note were found at either operation, so that the assumption of a meningitis would be without a history of this affection and without any anatomical evidence of its existence. The most plausible explanation of the cause of this condition is the congenital failure of the large branches of the cisternæ to develop. In the preceding case it is possible that the cisternæ may have been obliterated rather than that the branches have failed to develop; in this case the cisternæ are well open, in fact they are greatly distended; under the mid-brain the cisterna is as large as one's index finger.

An external hydrocephalus differs from the above picture only in that the fluid is distributed over the hemispheres instead of being confined to a localized cyst of more restricted size. In fact, in this case the hydrocephalus was transformed into an external hydrocephalus merely by opening the cyst, but the fluid, passing over the arachnoid membrane instead of under it, poured into the subdural space instead of the subarachnoid space, where there was only a slight absorption. The pathology of this case really forms a connecting link which explains the relationship between external hydrocephalus and internal hydrocephalus; this relationship and the general subject of external hydrocephalus will be considered in detail in a forthcoming publication.

[12] A description of the remarkable anatomical changes in this case would only add confusion if presented here. They are therefore omitted and will appear in a subsequent publication dealing with other phases of hydrocephalus. My purpose here is to correlate all the anatomical variations of communicating hydrocephalus into a single disease with a fundamentally similar pathology and etiology.

Obstruction of Some But Not All of the Main Branches of the Cistern.e

In the accompanying ventriculogram (Fig. 14) evidence of a very early hydrocephalus will be seen. It developed in a three-year-old child under observation in the service of Professor Howland. She was first treated for a typical illness of acute meningococcus meningitis, from which there was an apparent recovery, though very shortly lethargy and vomiting ensued. Six weeks after the onset of the attack of acute meningitis and two weeks after apparent recovery,[13] hydrocephalus was first suspected. At this time, the cell count in the cerebrospinal fluid was ten. The sutures of the skull were separated; a suggestive cracked-pot sound was obtained. There was no choked disc and no other sign of intracranial pressure. Without the ventriculogram the diagnosis of hydrocephalus could never have been substantiated. With the absolute verification it is probably the earliest recorded case of hydrocephalus. The ventriculogram was different from that of any previous case which has come under my observation. Air passed from the ventricles and finally reached the cerebral sulci, but only in a very restricted segment over the frontal lobe. Such a finding might have been assumed to be due to an imperfect injection of air, but one month later another ventriculogram was made and precisely the same segment of subarachnoid space and exactly the same sulci were injected. In this interval of 30 days between the two ventriculograms, the lateral ventricle had increased in size (compare Figs. 14 and 15), though the rate of growth was considerably less than in the usual development of hydrocephalus. The phenolsulphonephthalein output from the spinal canal rose from 13 per cent to 22 per cent; the latter percentage was found at the time the first ventriculogram was made; unfortunately, no test was made when the second ventriculogram was obtained. It is evident, from the phenolsulphonephthalein test, that a partial compensation has occurred, for, with 22 per cent absorption (normal 35-50 per cent), the hydrocephalus could not be full-blown. The ventriculogram was also interpreted to mean that the filling of part of the subarachnoid spaces denoted that a greater amount of cerebrospinal fluid (12 per cent more by the phenolsulphonephthalein test) than in the usual quantitative absorption in communicating hydrocephalus with an obstruction in the cisterna was being absorbed in this restricted area and that a partial compensation had developed, as it should have done.

[13] A pneumococcus panophthalmitis also developed, necessitating removal of the eye, from which the meningococcus was grown in pure culture.

The branches of the cisternæ can be traced directly from the cisterna chiasmatis to the cerebral sulci of the frontal region. Numerous perpendicular air shadows are clearly shown just above the cisterna interpeduncularis and rising vertically from it but ending blindly. These shadows, I believe, represent the branches of the cisternæ which are obstructed and which should supply the remainder of the cerebral hemispheres with fluid. The air extends in these branches up to the point of the obstruction in each individual branch (Fig. 14).

This patient has been seen at intervals for the past two years and has recovered completely. We have proof from the pneumographic records not only of the existence of a hydrocephalus, which could not have been diagnosed otherwise, of its unusual rate of development, and of its spontaneous cure, but, more important, we have the findings in the transition stages and, we think, the reason for the compensation and eventual cessation of development of the hydrocephalus. Whether at one time *all* the cisternal branches were occluded and *some* subsequently opened, producing a partially compensating hydrocephalus: whether additional spaces were reestablished after our studies were made and permitted the condition to change from a partially compensating hydrocephalus to a complete cure, we have not the pneumographic evidence to prove or disprove.

I do not believe that it is possible for a hydrocephalus to occur, if all or even many of the cerebral sulci can be shown to fill with air or if the phenolsulphonephthalein output after a spinal injection measures 35 per cent in two hours. From a large series of cases of hydrocephalus, there has been no exception to disprove this statement. We are, however, not yet sufficiently familiar with the roentgenographic pictures of the cerebral sulci to make many positive claims as to prognosis in these unusual types of hydrocephalus.

SUMMARY AND CONCLUSIONS

(1) The cerebrospinal fluid circulates in a closed vascular system. This is just as well defined as the vascular system for blood, lymph, bile or urine.

(2) The ventricular system, in which fluid is produced but not absorbed, is lined with a high cubical and columnar epithelium; the subarachnoid space, in which the cerebrospinal fluid is absorbed, is lined with low mesothelial cells. Nearly all the cerebrospinal fluid is absorbed in the cerebral sulci.

(3) Collateral circulation is almost precluded either in the ventricles or in the cisternæ. An obstruction in these spaces, therefore, results in a hydrocephalus, just as closure of a ureter results in a hydronephrosis. If the obstruction is situated in any part of the ventricles (usually the aqueduct of Sylvius or the foramina of Luschka and Magendie) the hydrocephalus is of the obstructive type; if it is situated in the cisternæ (or in the main branches of the cisternæ) it is of the communicating type.

(4) That the cause of communicating hydrocephalus (the remnant of so-called idiopathic hydrocephalus) is an obstruction in the cisternæ is conclusively demonstrated in three ways. (a) Experimentally communicating hydrocephalus can be produced by blocking the mesencephalic cisterna. (b) The obstruction can be graphically demonstrated in the experimental animal or at necropsy in the human by injecting a suspension of India ink into the spinal canal: the color stops abruptly at the obstruction. (c) In all living patients the obstruction can be clearly shown by cerebral pneumography after air has been injected into the spinal canal; the air also stops at the obstruction, and can be sharply outlined in the roentgenogram.

(5) The obstruction in the subarachnoid space is most frequently located in the mesencephalic or pontine cisterna.

(6) However, the obstruction need not necessarily be in the cisternæ; it may be in the large branches which carry the fluid from the cisternæ chiasmatica and interpeduncularis to the cerebral sulci. Any number of these branches may be occluded. If all the main branches are obstructed, the hydrocephalus will be the same as if the occlusion were in the cisterna. If some of the branches remain unobstructed, the degree of hydrocephalus will be modified proportionately; a complete cure may even result because of the absorption which takes place in the remaining patent areas of the subarachnoid space.

(7) Adhesions, which follow meningitis and occlude the cisternæ, cause the vast majority of cases of communicating hydrocephalus. They also cause many cases of obstructive hydrocephalus, by blocking the foramina of Luschka and Magendie. Adhesions give infallible proof of a preexisting meningitis. A history of meningitis may be easy, difficult or impossible to obtain. The post-meningitic occlusions have no relation to the severity of the attack and the number of adhesions but rather to the location of the adhesions.

(8) In two cases the hydrocephalus appeared to be due to a congenital failure of the cisternæ or of its branches to develop. Tumors in the pons, medulla, or mid-brain also produce partial or complete obstruction of the subarachnoid space and therefore cause communicating hydrocephalus.

(9) Pneumographic records are shown demonstrating the existence of a very early stage of communicating hydrocephalus, the cause of the hydrocephalus, the reason for its unusually tardy development, and for its spontaneous arrest.

DESCRIPTION OF PLATES

FIG. 1.—The mesencephalic cisterna is completely blocked in a dog by surrounding the mid-brain with a piece of gauze saturated with iodine. The lower figure shows a section of the mid-brain with the gauze band in place. The band is between the margins of the incisura tentorii and the surface of the mid-brain. Communicating hydrocephalus follows this experimental procedure: the reasons for the hydrocephalus will be seen in Figs. 3 and 4.

FIG. 2.—Section of a dog's brain to show the grade of hydrocephalus which resulted from the perimesencephalic band of adhesions (Fig. 1). On the right is a section of a normal brain as a control. The hydrocephalus is of three months' development.

FIG. 3.—Drawings by Max Brödel to give a graphic demonstration of the reason for the development of communicating hydrocephalus after the formation of the perimesencephalic adhesions. India ink had been substituted for cerebrospinal fluid in the spinal canal two hours before the animal was sacrificed. On the right is a control

animal in which the same quantity of ink was injected at a similar time before death. In each case the ink has had the distribution which the cerebrospinal fluid would have. In the normal (right), the ink has thoroughly and evenly covered every part of the brain's surface because all of the cerebrospinal spaces receive the cerebrospinal fluid. In the experimental animal the ink has stopped sharply at the perimesencephalic band. None of the ink has been able to reach the cerebral hemispheres, although the cerebellum has been as well covered as the normal. In Fig. 2 it will be seen that in the normal brain the ink has not entered the lateral ventricles, whereas in the experimental animal the ventricles have filled with ink. Since the ventricles fill with ink, there can be no question that the injection is inadequate, for the ventricles are farther forward than the obstructing band.

FIG. 4.—Dorsal view of the same brains (as Figs. 2, 3) to show the distribution of the ink on this surface. It will be seen that the ink has not extended beyond the tentorium (owing to the perimesencephalic band), whereas in the normal the entire brain is covered. Hydrocephalus results from this band because the trunk of the subarachnoid tree is occluded and cerebrospinal fluid cannot reach the spaces over the cerebral hemispheres where most of the cerebrospinal fluid absorbs.

FIG. 5.—Drawing by M. Brödel to show the general plan of the vascular system for cerebrospinal fluid. Fluid forms in the cerebral ventricles and is absorbed in the subarachnoid space. The paired foramina of Luschka and the median foramen of Magendie are the only openings by which the ventricular fluid can leave the ventricles and reach the subarachnoid space. Obstructions at these openings, the aqueduct of Sylvius or at the foramen of Monro produce hydrocephalus involving the ventricles anterior to the obstruction. Obstructions in the subarachnoid space are just as effective in producing hydrocephalus. The sites of these obstructions and their effects will be shown in the succeeding diagrams.

FIG. 6.—Pneumogram (intraventricular injection of air) to show normal ventricle and normal subarachnoid spaces. Note that the cerebral sulci (the wavy lines) are filled over the entire surface of the brain. The cisternæ interpeduncularis and chiasmatica are shown as the distributing center from which all the cerebral sulci receive their fluid.

FIG. 7.—Diagram to show the disturbance in the circulation of cerebrospinal fluid following an obstruction at the mesencephalic or pontine cisterna. The black area represents the absorbing spaces, which cannot be reached by the cerebrospinal fluid owing to the obstruction. Hydrocephalus results because this vast area (where three-quarters to four-fifths of the cerebrospinal fluid is normally absorbed) can no longer perform its function. The mesencephalic and pontine cisternæ are the usual sites for post-meningitic obstructions in communicating hydrocephalus. A pneumogram of this type of obstruction is shown in Fig. 9. Fig. 8 shows a patient with this disease and having an occlusion at this point; Fig. 10 shows the ventricular system of this patient filled with air. Figs. 9 and 10 show this obstruction demonstrated clinically by the intraspinous and intraventricular methods, respectively. Figs. 11 and 12 show the pathology of this type of hydrocephalus.

FIG. 8.—Photograph of a patient with communicating hydrocephalus following meningitis. The marked retraction of the head and neck has persisted long after the acute illness has subsided. The ventriculogram of this patient is shown in Fig. 10.

FIG. 9.—Cerebral pneumogram (retouched) of a case of communicating hydrocephalus; air has been injected into the spinal canal. The obstruction is at the mesencephalic cisterna (*cf.* arrow). No air has reached the cerebral sulci but the lateral ventricle has been partially filled by the retrograde flow of air through the dilated foramina of Luschka and Magendie. Compare this *intra vitam* demonstration of the causative lesion with that shown *post mortem* by the injection of ink (Figs. 17 and 18) or with the example of experimental hydrocephalus (Figs. 2, 3, and 4). *A* = cisterna pontis. *B* = cerebellar subarachnoid space. *C* = cisterna magna. *V* = lateral ventricle.

FIG. 10.—Untouched reproduction of a ventriculogram from a case of communicating hydrocephalus (shown in Fig. 8); 800 c. c. of fluid were aspirated and an equal quantity of air substituted. The entire cerebrospinal vascular system is shown in the pneumogram up to the point of obstruction, which is also sharply defined. The tremendous lateral ventricles have lost all semblance of their former shape and practically fill the huge cranial chamber. The third ventricle, the aqueduct of Sylvius, and the fourth ventricle are outlined sharply. The foramen of Magendie can be seen; the large cisterna magna fills much of the posterior cranial fossa. The obstruction which is causing the hydrocephalus is at the anterior terminus of the shadow of the cisterna magna. The obstruction, therefore, is in the cisterna pontis; no air has reached the cerebral sulci. The hydrocephalus in this case followed an attack of epidemic meningitis. *V* = lateral ventricle. *III* = third ventricle. *IV* = fourth ventricle. *P* = suprapineal recess of third ventricle. *A.S.* = aqueduct of Sylvius. *M* = foramen of Magendie. *C* = cisterna magna. *X* = obstruction in pontine cisterna. This obstruction causes the hydrocephalus.

FIG. 11.—Inferior surface of the brain of a case of communicating hydrocephalus; the mid-brain has been divided transversely and the cerebellum and brain stem removed. Note the large aqueduct of Sylvius *B* and the large tumor-like dilated third ventricle *A* which compresses the optic nerves and destroys the sella tursica just as a hypophyseal tumor would do. Such a protrusion of the third ventricle is not always present in hydrocephalus.

FIG. 12.—Inferior surface of the brain stem and cerebellum of the above case (Fig. 11). The foramen of Magendie is entirely closed by adhesions. The right foramen of Luschka is patent (reader's left) as indicated by the probe *L* which easily passes through it from the fourth ventricle. The left foramen of Luschka (reader's right) is sealed and protrudes as a bulging cyst. The probe which is introduced into the lateral recess of the fourth ventricle of this side meets this obstructing membrane. The dilated cystic pouch (foramen of Luschka) is surrounded by a series of arrows in order to identify it.

FIG. 13.—Diagram showing the effect on the cerebrospinal fluid circulation when some, but not all, of the branches from the cisternæ interpeduncularis and chiasmatica are occluded. The black area represents the subarachnoid space which does not receive cerebrospinal fluid. In the clear zone the circulation is intact. Figs. 14 and 15 are pneumographic records of such a type.

FIG. 14.—Photograph of roentgenogram of head after the injection of air into ventricle (not retouched). This patient had an early hydrocephalus following acute cerebrospinal meningitis. Only a small number of the cerebral sulci contain air (bracket between x and x). The obstruction which caused the hydrocephalus was not in the cisternæ but in the large branches which carry the cerebrospinal fluid from the cisternæ to the sulci. The arrow points to the cisternæ and the dilated obstructed branches; *C* = cisterna magna. The shadow of the mesencephalic and pontine cisternæ can be followed through the dense petrous bone. The partial filling of the cerebral sulci (x to x) explains the slow development of the hydrocephalus and its subsequent spontaneous cure. Fig. 15 is a ventriculogram of the same case 30 days later.

FIG. 15.—Pneumogram of above case (Fig. 14) 30 days later. The increase in size of the ventricle is clear and easily measurable, but it is of a moderate grade. Exactly the same sulci are injected and the same dilated cisternæ interpeduncularis and chiasmatica and the same dilated obstructed branches are shown.

FIG. 16.—Diagram showing the effect upon the cerebral subarachnoid space when all the main branches, which carry the fluid from the cisternæ interpeduncularis and chiasmatica, are occluded. Exactly the same absorbing area is eliminated and the hydrocephalus which results is identically the same. In our cases of this type absence of these branches was regarded as probably due to a congenitally defective development of these spaces. Fig. 20 is a ventriculogram of this

FIG. 1.

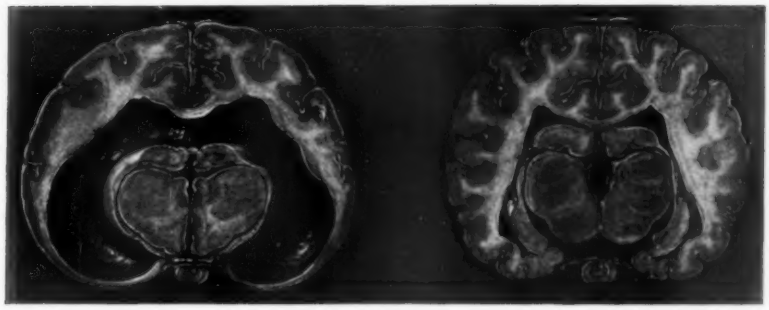

FIG. 2.

FIG. 3.

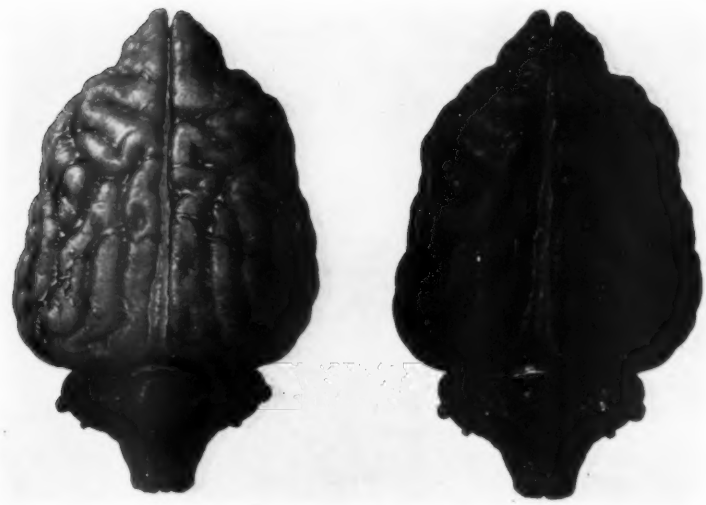

FIG. 4.

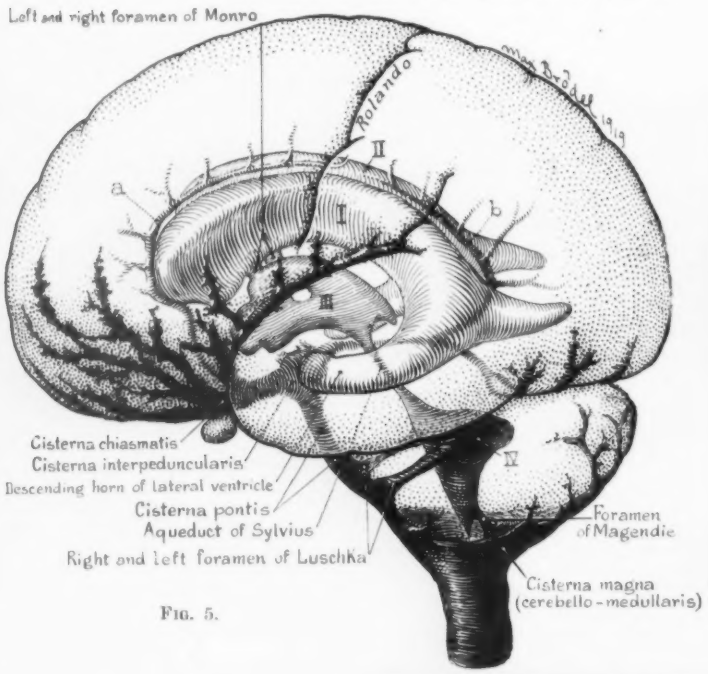

FIG. 5.

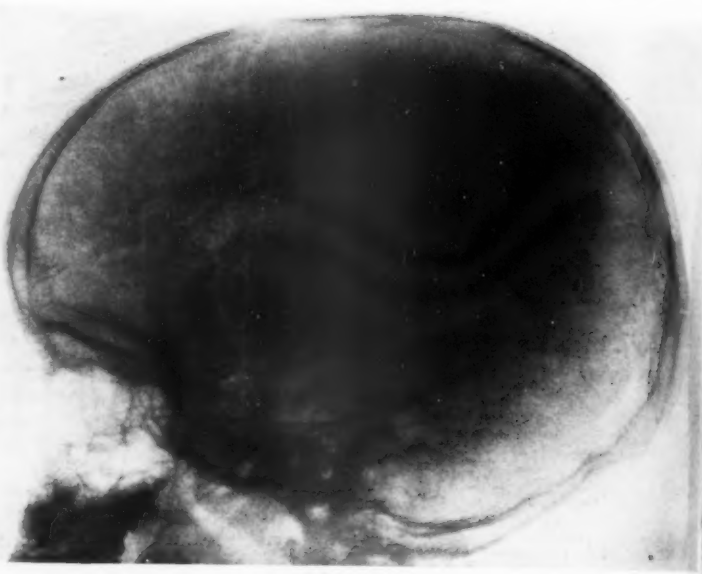

FIG. 6.

FIG. 8.

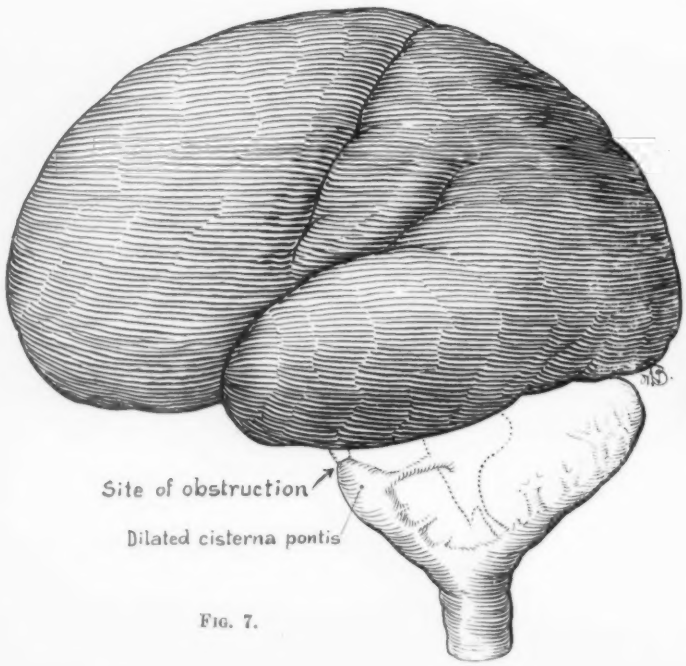

FIG. 7.

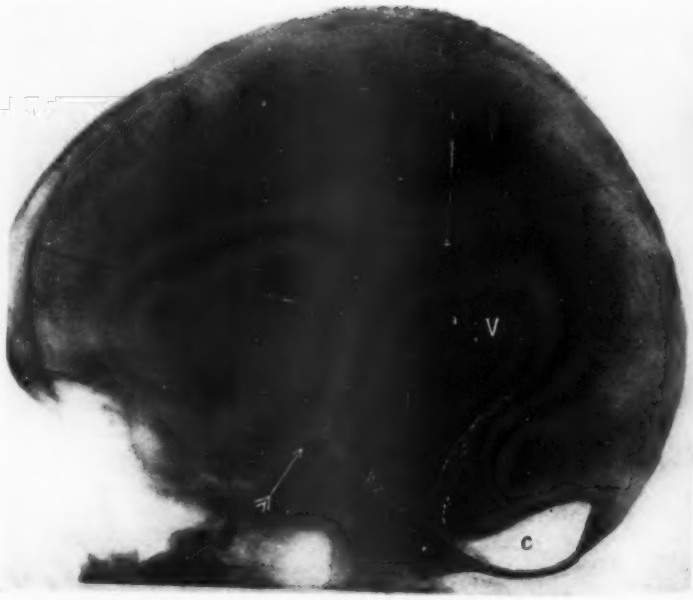

FIG. 9.

FIG. 10.

FIG. 11.

FIG. 12.

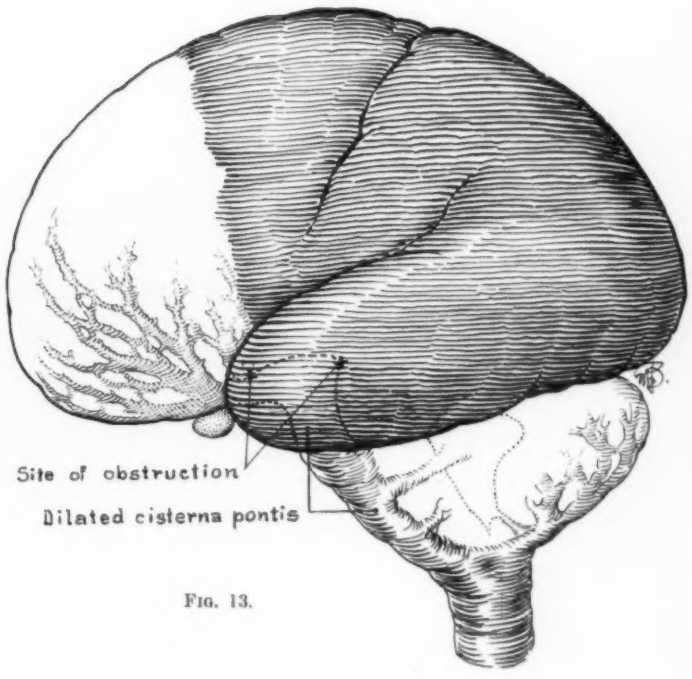

FIG. 13.

FIG. 14.

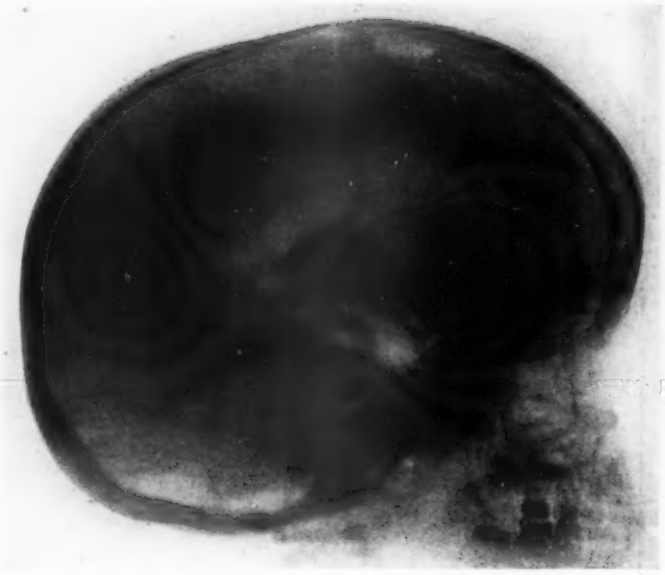

FIG. 15.

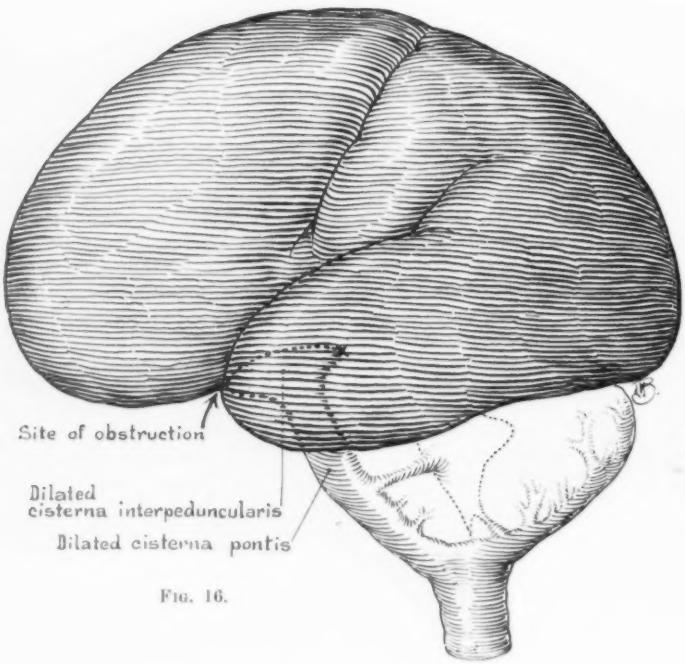

FIG. 16.

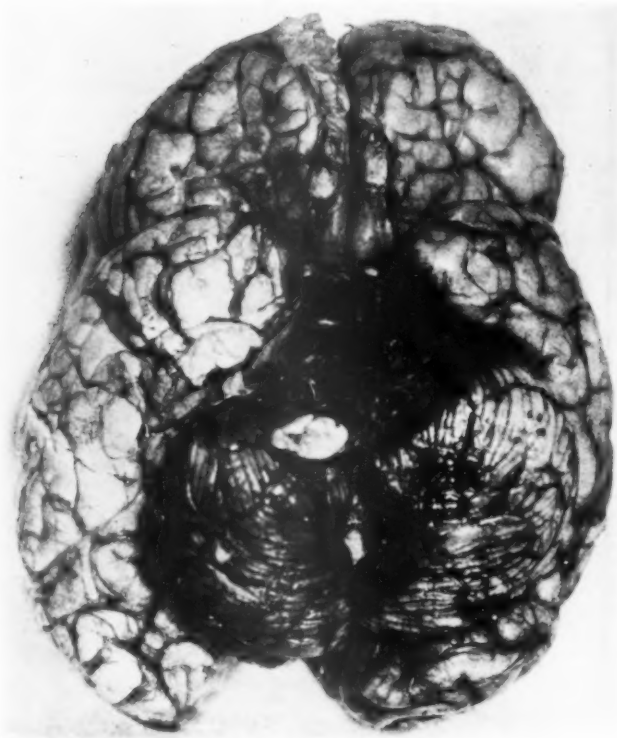

FIG. 17.

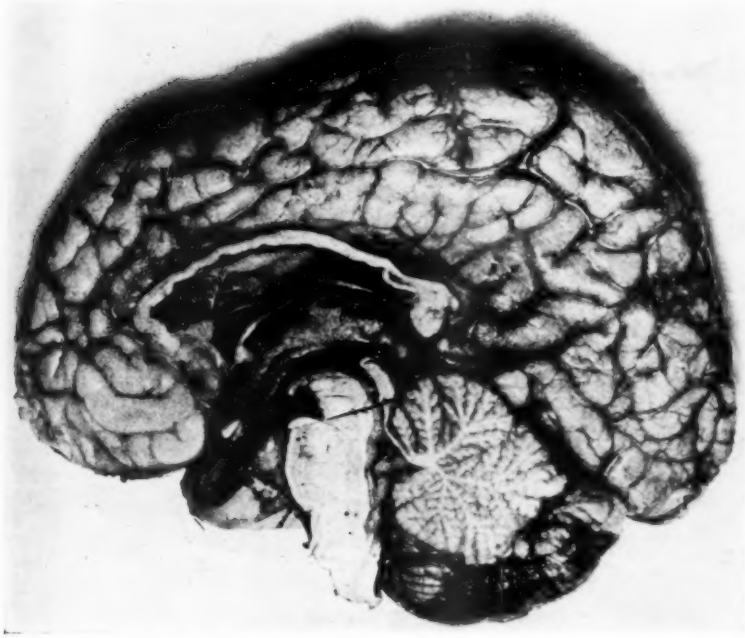

FIG. 18.

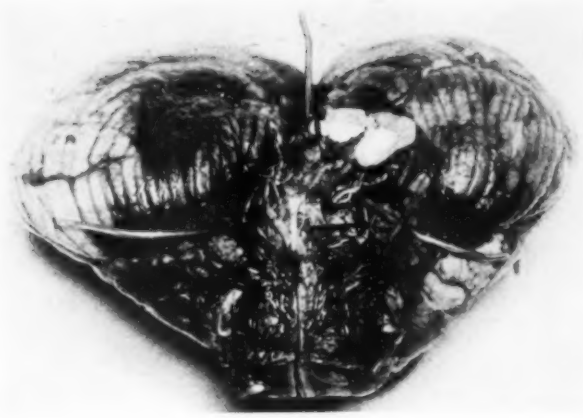

FIG. 19.

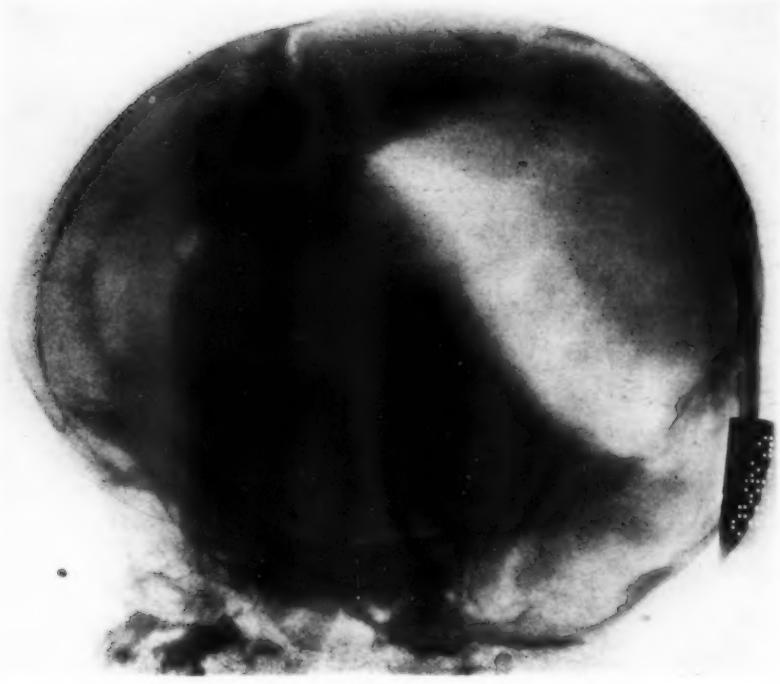

FIG. 20.

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[In the description of figures which have been made from the fetal bones examined, the number CC indicates the number of the specimen in the Embryological Collection of the Carnegie Institute.]

1. Fetal osteochondritis luetica. Roentgenogram from the distal end of the femur. Fetus CC No. 2333. This picture shows excessive calcification.

2. Hand and forearm of human fetus (CC No. 2300) to show extreme excessive calcification of the provisional area with irregular prolongation of the provisional calcified zone into the area of proliferative cartilage. Note the presence of the same lesions in the metacarpals and phalanges.

3. Radius and ulna from human fetus (CC No. 2186) showing beginning resorption of the area of intense calcification at the epiphyseo-diaphyseal junction. Resorption shown by areas of decreased density of shadow, each resorptive area surrounding a small nucleus of persistent trabecular tissue.

4. X-ray picture of syphilitic osteochondritis of the bones of the hand and forearm of a human fetus (CC No. 2044) showing a zone of rarefaction between two lines of abnormal calcification. Note the lesion in the phalanges and metacarpals.

5. Human fetus (CC No. 2350). Luetic osteochondritis of the distal end of the femur. This bone shows an abnormally heavy calcification of the provisional area of calcification separated proximalward by a narrow line of rarefaction from the broad band of dense shadow cast by fine closely set trabeculæ at the epiphyseal end of the shaft.

6. Third stage (Wegner) of luetic osteochondritis of the distal end of the femur and proximal ends of tibia and fibula. Human fetus CC No. 2643. This is the picture which immediately precedes epiphyseal separation. A wide band of syphilitic tissue separates the irregular broad spotty zone of provisional calcification from the distal end of the diaphysis.

7. Syphilitic periostitis of both bones of the forearm of fetus CC No. 2597. Note the longitudinal striation of the thick periosteal shadow which is nearly in contact with the shafts of the bone.

8. Syphilis of the femur. Human fetus CC No. 2513. Showing separation of the cortex from the spongiosa.

9. Distal end of radius and ulna of Case I. This plate shows intense calcification of the provisional zone with resorption areas on the marrow side of the epiphyseal line. Both bones show syphilitic periostitis and there is separation of the cortex from the spongiosa in the ulna.

10. Radiogram of the distal ends of the radius and ulna of Case II. This shows a syphilitic osteochondritis with marked areas of resorption and a mild grade of periostitis.

11. Roentgenogram of the proximal ends of the tibia and fibula of Case III, showing syphilitic osteochondritis with over-calcification of the provisional calcified zone with a Trümmer-zone-like area behind it and a mild grade of periostitis of the tibia.

type of obstruction. Figs. 17 and 18 show the obstruction as defined by an intraspinous injection of ink.

FIG. 17.—Base of brain of a case of communicating hydrocephalus. Ink has been injected into the spinal canal before necropsy. The black coloring extends along the cisternæ to the optic chiasm. It has covered the cerebellum but none of the cerebral hemispheres. (The black shadow over part of the left temporal lobe (reader's right) is due to a post-mortem hæmatoma and not to the ink.) Compare this post-mortem demonstration of the obstruction with a pneumographic demonstration (Fig. 9) during life and with the experimental lesion (Figs. 1, 2, 3, and 4).

FIG. 18—Sagittal view of the above brain (Fig. 17). The ink is seen deeply staining the walls of the third and fourth ventricles and the aqueduct of Sylvius, although none of the color reached the surface of the cerebral hemispheres. The aqueduct of Sylvius and the foramen of Magendie are patent and enlarged, thus demonstrating that the hydrocephalus is of the communicating type. Compare the intraventricular distribution of ink in the experimental animal (Fig. 2).

FIG. 19.—Cerebellum and brain stem of the above case (Figs. 17 and 18). The three wires are intended to show that the three foramina (Luschka and Magendie) are open. On the right side the wire had slipped out and was replaced by the photographer, who thought it had been properly reinserted. The foramen is seen *under* the wire, the border of the foramen being indented by its pressure; the actual foramen of Luschka can be seen in the circle of arrows; the flocculus emerges from the foramen of Luschka on each side.

FIG. 20.—Ventriculogram of a case of communicating hydrocephalus due to occlusion of the main branches of the cisternæ interpeduncularis and chiasmatica. The larger two-finger-like process projecting into the ventricle is a huge cyst, which is a direct outgrowth of the cisternæ interpeduncularis and chiasmatica. The elucidation of the findings was possible by a thorough inspection of the base of the brain at operation. Owing to pressure on the aqueduct of Sylvius the circulation of air from the lateral ventricles was restricted; therefore, the cyst, the fourth ventricle and the cisternæ did not immediately fill with air following the intraventricular injection.

X-RAY PICTURES OF THE BONES IN THE DIAGNOSIS OF SYPHILIS IN THE FETUS AND IN YOUNG INFANTS

By P. G. SHIPLEY, J. W. PEARSON, A. A. WEECH

AND

C. H. GREENE

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For some time past it has been quite generally recognized that but little dependence could be placed on the Wassermann test during the early weeks of life as an aid to the diagnosis of syphilis. A positive Wassermann is still regarded as nearly specific but a negative serum test no longer is allowed to free the newly born child or young infant from suspicion of luetic infection. Certainly this is true until the end of the second month of life is reached and there is a growing tendency to extend the period of capricious serum reaction to the end of the fourth month. Indeed there is so little expectation of obtaining a positive complement fixation reaction from the blood of newly born children that in the obstetrical service of at least one of our large teaching hospitals[1] the routine syphilological examination of blood from the cord of the newly born babies is regarded as not repaying the trouble and expenditure involved in carrying out the technique.

The diagnosis of lues in the newly born or very young child is not by any means always easy, since clinical symptoms of the disease may be, and in fact are usually, entirely absent from the child until several weeks after birth. Moreover, a mother without a single clinical manifestation or any serological indication of spirochætal infection may give birth to a luetic infant.

Under such conditions, when any addition to the diagnostic armamentarium against the disease in young children might be welcomed, it seems rather surprising that so little attention has been paid to the routine use of a method which has the advantage of rapidity and ease of application—the examination of the bones by means of the X-ray.

It has long been a matter of common knowledge that the skeleton is among the tissues most frequently affected by the luetic process during intra-uterine life and as early as 1870 Wegner described three stages of osteochondritis syphilitica. Moreover, the alterations in the affected bones are easy of recognition in the X-ray picture and when present are pathognomonic.

Every syphilitic infant does not show bone lesions on X-ray examination, but cases are not infrequent among young children in which roentgenography discloses evidences of lues when no clinical or serological data are available for diagnosticating the presence of the infection. Our experience has led us to believe that routine examination of the osseous system in newly born children will yield valuable diagnostic data and insure recognition of the presence of a hereditary infection in a certain number of children who otherwise might go on unaided for several months before some clinical symptom or the accidental discovery of a positive serum reaction would secure for them the much needed therapy.

We have had the opportunity of examining some 300 white fetuses ranging in age from the sixth month of intra-uterine life to nearly term with the object of securing as many variations as possible of the normal and pathological skeletal X-ray pictures. The fetuses were of white parentage and were listed as normal in the catalogue of the Carnegie Institute of Embry-

ology, from which collection they were taken.* Incidentally, the examination of the plates taken of these specimens furnished a striking demonstration of the terrible toll claimed by syphilis during intra-uterine life.

Out of the first 100 plates studied, representing the same number of white male fetuses, 15 showed advanced luetic osteochondritis, 10 had signs of less marked syphilitic involvement and 21 showed one or more bones which presented slight variations from the normal picture and were noted as suspicious. In other words, the skeletons of 25 per cent had marked signs of lues and 46 out of the first 100 bodies examined had well-marked or suspicious lesions.

The syphilitic lesions seen in the bones of children are roughly of two types, those seen in newly born and young infants and those which characterize syphilis of the osseous system of older children. We shall not attempt to discuss here those of the latter variety and, since those which it is necessary to recognize in infants and newly born children are essentially of the fetal type, a detailed knowledge of the lesions encountered in the fetus is most important in the routine use of the X-ray picture as a diagnostic method.

If one examines an X-ray picture of a normal fetus or newly born child, it will be seen at once that while the shadow cast by the diaphysis is sharply outlined, the epiphyseal cartilage is invisible, since its density is approximately equal to that of the surrounding soft parts. The cortex of the shaft, which is usually of unequal width according to the curvature of the bone, is thickest at the plane of entrance of the nutrient canal and from this point it tapers in either direction to hair-line thinness at the epiphyseo-diaphyseal junction. In the central canal of the bone the marrow space is very small and one sees the spongiosa made up of sharply cut, fine, regularly ordered trabeculæ arranged in the form of a framework for the homogeneous marrow spaces about the circulatory system of the bone. The nutrient canal, through which the blood vessels enter the bone, is easily made out and can be seen to divide into two branches just beneath the cortex. The bony trabeculæ become finer and finer as the epiphyseo-diaphyseal junction is approached and end abruptly in a more or less curved, or straight, but always clear-cut line which is so sharply drawn as to appear to be ruled. They may terminate in a fine granular line running at right angles to their long axes (the calcified intracellular substance of the epiphyseal cartilage) but usually the individual trabecula may be distinguished throughout its entire length.

Syphilitic bones throw quite a different and characteristic shadow on the photographic plate after exposure to the X-ray. Usually all the bones are not affected to the same extent and some of them may have apparently escaped entirely. Those which are most often or most severely affected are in order of frequency the lower end of the femur, the distal and proximal ends of the tibia, the distal ends of the radius and ulna, the extremities of the metacarpals, the proximal ends of the phalanges, and the proximal ends of the ulna and radius. No bones are exempt from the syphilitic changes; even the bodies and processes of the vertebræ, the ribs and the bones of the skull do not escape.

The shadows resulting from syphilitic lesions in early life are due to vagaries in the calcification of the provisional cartilage and to the abnormal arrangement and distribution of osseous tissue. The syphilitic changes in the bones of the fetus, unless they are very severe and of long standing and the fetus is close to term, do not involve the periosteum to any demonstrable extent but are confined to the epiphyseo-diaphyseal region. At any rate in the fetal type of reaction the periosteal lesion is secondary in importance to the endochondral defect. After birth the periosteal reaction begins, possibly because of the increased demands made on this tissue by the increased muscular activity, and in young infants this may be the most marked skeletal lesion.

The beginning of the process as shown by the X-ray picture is an intensification of the shadow cast by the bone at the epiphyseal line. This line becomes much broader and more homogeneous and seems to form a cap on the ends of the trabeculæ of the spongiosa (Fig. 1). This is significant of the beginning of abnormally heavy calcification of the provisional calcified zone. It must be remembered that while the provisional zone of calcification in the cartilage of the normal embryonic bone is, relatively speaking, very narrow, in many cases only one or two cells deep, in the syphilitic bone the calcified cartilage may show on section a width of from 0.5 mm. to 1.5 mm.

In other bones in which the osteochondritis is further advanced, it can be seen that on the marrow side of the intensified shadow of the provisional zone there is a band-like area where the shadow is less intense than in the rest of the bone (Fig. 3), giving an appearance of diminished density to the region of the epiphyseal line.

Bones may also be seen in which the dense shadow at the epiphyseal end of the bone is broken by the presence of one or more small areas of rarefaction so as to give an appearance of irregular density to the end of the bone (Fig. 3).

At other times the bone appears to end in a double line, so that two lines of heavily calcified tissue are seen, separated each from one another by a zone in which lime salts are less heavily deposited. This zone is a region which histological preparations show to contain a great deal of delicate granulation tissue. This picture becomes more and more intensified as growth goes on. The areas of dense shadow and the fine clearer band between them grow wider and the surfaces bounding them become more and more irregular and jagged till the end of the bone has an irregular, ragged appearance (Figs. 4, 5, 6). During the course of the disease the calcification of the infected areas is not only abnormally heavy but also most irregular, so that the epiphyseal border of the shadow cast by

* We have here to express our gratitude to Dr. Geo. Streeter, director of the Laboratory of Embryology of the Carnegie Institute, for permission to use this material, and to Miss M. S. Smith of the X-ray Department of The Johns Hopkins Hospital for the time and care spent in making excellent X-ray plates from most difficult material.

the bone has a notched, saw-toothed or serrated appearance (Fig. 2).

Practically all the bones are involved by the luetic process and it has been shown by Alexander,[2] who has studied the roentgenography of osteal syphilis with great care, that luetic changes can be demonstrated in the excised ribs, in the scapula, vertebral bodies and processes and in the bones of the skull base and pelvis. About the various centers of ossification in the different bones of the body the syphilitic picture is beautifully drawn. The nucleus becomes surrounded by a very wide zone of provisional calcification and eventually becomes doubly contoured by the development of a pericentral ring of tissue which casts but little shadow.

The phalanges, metacarpals and metatarsals give characteristic pictures of luetic osteochondritis and are affected by the spirochæte with surprising regularity and to a very marked degree (Figs. 2, 3, 4). The metacarpal and metatarsal bones show the lesion at either end, but the phalanges, because of the manner in which they are developed, are affected only at the proximal extremities.

Periostitis when it occurs near term in the severe cases of lues may be present throughout the length of the bone or only at the extremities. It is shown in X-ray plates by a more or less wide, almost homogeneous, shadow or with longitudinal striations separated from the external surface of the cortex by a narrow clear area which bounds the bone (Fig. 7).

One other feature of these pictures appears worth noting. It may be seen that in many luetic bones the cortex is separated from the spongiosa by a very narrow clear zone which gives the cone of spongy bone the appearance of being suspended unattached within the cortical cavity (Fig. 8). In the X-ray picture the trabeculæ of the syphilitic bone appear to be finer than those of the normal bone.

With these facts in mind it will be seen that osteal syphilis may be easy of recognition even in the fetus and that X-ray studies, if employed as a routine, may be at times a valuable aid in the early diagnosis of hereditary lues.

The following cases serve to illustrate the value of the procedure:

CASE I.—M. D., colored, female.

First seen in the out-patient department of the Harriet Lane Home on April 19, 1918, at the age of 5 weeks with the complaint that she did not use the right arm well. There were no signs of syphilitic infection and nothing in the history to suggest hereditary lues. The Wassermann test was negative, but the X-ray picture (Fig. 9) of the bones of the forearm showed a slight degree of periostitis and a well marked syphilitic osteochondritis of the radius and ulna. *Diagnosis.*—Syphilis, hereditary, early (epiphysitis).

CASE II.—H. R., white female infant, aged 6 weeks.

Came to the out-patient service at the Harriet Lane Home September 30, 1920, with a slightly swollen wrist-joint. There was no suggestion of any syphilitic history and examination for signs of the disease was without result. Repeated Wassermann tests were negative, but the X-ray plate of the swollen wrist (Fig. 10) showed a syphilitic osteochondritis with a very intense grade of resorption behind the epiphysis. This child was given antisyphilitic medication and the family kept under observation. It was possible to obtain blood from both the mother and father of the patient and a Wassermann reaction was done in duplicate in two different laboratories on both parents, once with serum from the father and twice with the mother's blood. Both laboratories returned a negative report on the paternal serum. The report on the mother's serum was twice returned by one laboratory as positive and twice negative by the other. The child is still under treatment with diarsenol and mercury and has shown marked improvement.*

CASE III.—K. P., white female child under observation in the out-patient department of the Harriet Lane Home since June 10, 1920, aged 2 months, with a diagnosis of hypertrophic stenosis of the pylorus. Physical examination was negative except for a somewhat enlarged spleen and a slightly swollen ankle. The child's Wassermann reaction was negative three times, on the 1st and 11th of November, and on the 2d of December, 1920. The mother's Wassermann was negative on the 11th of November. The X-ray picture of the swollen leg (Fig. 11) showed syphilitic osteochondritis of both proximal and distal ends of the tibia and fibula. Since November 2d the child has improved under treatment with mercury and diarsenol.

Two other conditions which are encountered in children may give X-ray pictures which closely resemble, and in some cases are identical with, the pictures described above. Scurvy and rickets, when the latter disease is healing under the influence of cod-liver oil therapy, may be difficult or impossible to differentiate by roentgenographic means from osteal syphilis of the fetal type. Fortunately, however, in the early weeks of life neither of these conditions need be seriously considered in diagnosticating hereditary lues, since there is no good evidence to show that fetal rickets ever occurs and it is agreed that scorbutus is rare before the sixth month of life has been reached.

In passing it is interesting to note that lues of the fetus and newly born child apparently, even in advanced cases, interferes very little, if any at all, with skeletal growth since the fetuses which we have studied were in all respects, as far as careful anthropometry could determine, of normal growth for the age which they had reached.

It is our purpose shortly to publish a series of studies in an attempt to correlate the pathology of the syphilitic bone with the shadow cast by it on exposure to the X-ray.

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* Since this case was under observation the father of the patient has been found to have an aortic aneurysm and is at present under treatment in the out-patient department of The Johns Hopkins Hospital.

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INTERNAL MIGRATION OF THE OVUM

By George W. Corner

(From the Station for Experimental Evolution of the Carnegie Institution, Cold Spring Harbor, Long Island, and the Anatomical Laboratory of The Johns Hopkins University)

In contemplating the passage of fertilized ova from the Graafian follicle to their resting-place in the uterus, observers have often been struck by the fact that an egg discharged from a given ovary may pass through the opposite tube, or when the uterus is bicornate, may actually find lodgement in the opposite cavity. Long tubular bicornate uteri like those of swine offer ready demonstration of migration of the ovum, for it is a very frequent observation indeed (about once in three cases) that one horn of a pregnant uterus contains more embryos, the other less, than the number of corpora lutea in the corresponding ovary. To cite one example of hundreds available, it was found in a certain sow (Fig. 1) that the left ovary contained seven recent corpora lutea, the right ovary two; the left uterine cornu four fetuses and the right five. Three of the embryos in the left uterine cornu had originated, therefore, in the right ovary. Like conditions have long been known in other animals with similar uteri.

In the human uterus, with its single cavity, migration of the ovum will not be detected except under peculiar conditions, but numerous clear cases have been described. In many tubal pregnancies the corpus luteum has been found in the ovary opposite to the pregnant tube; for an especially convincing case of this type the reader is referred to one reported by Williams (1917). Migration has also been seen in cases of pregnancy in bicornate uteri, and offers at least a plausible explanation of cases such as those reported by Kelly (1906) and Winckler (1905), in each of which one ovary and the opposite tube were removed, but nevertheless the patients subsequently became pregnant.

The frequency of migration of the ovum in the human subject is not known, but may be crudely estimated by various means. Mayrhofer (1876) considered that migration must occur at least once in 10 ovulations. The present writer (Corner, 1915) found from a study of 128 pregnancies in swine that in this species one or more ova migrate in at least one-third of all cases. An exact statement cannot be made because the data are obscured by non-development of one or more embryos in four-fifths of the litters.

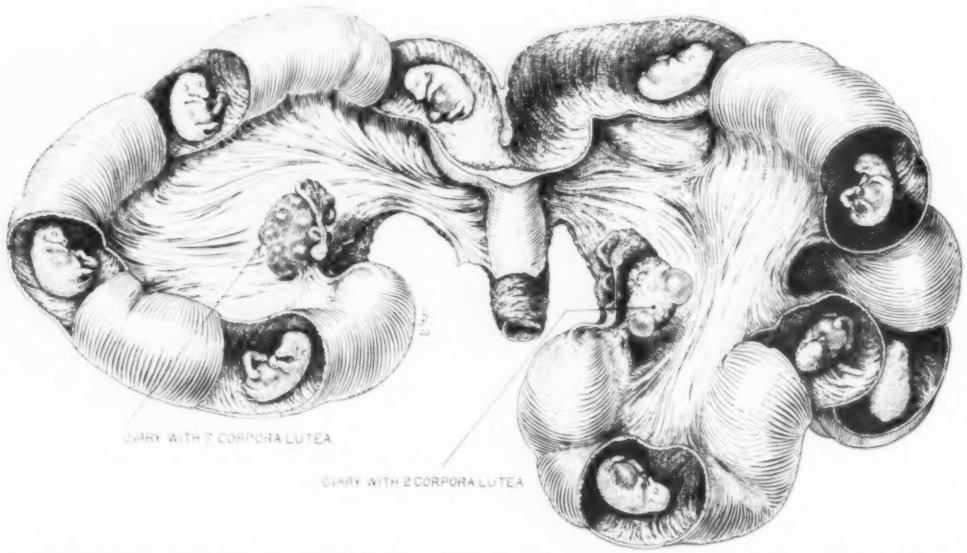

FIG. 1.—Ovaries and uterus of pregnant sow in which migration has occurred. Seven corpora lutea in left ovary, two in right ovary; four fetuses in left cornu, five in right cornu. One-fourth natural size.

It is obvious, as first pointed out by Kussmaul (1859), that there are two possible pathways of migration. Either the ova pass from the ovary into the abdominal cavity and thence directly into the opposite tube (external migration, Fig. 2.) or they travel by way of the homolateral tube into the uterus and thence to the place of implantation in the contralateral uterine cornu or Fallopian tube (internal migration, Fig. 3). External migration is not possible in those mammals in which the distal portion of the tube forms a closed pouch or ovarian capsule about the ovary, as in the rat (Fig. 4) and guinea-pig; but no such anatomical bar exists in man, rabbit or cat, in which the tubal extremities open freely into the abdominal cavity. In these animals it is conceived that the possibility of external migration is further enhanced by the action of the

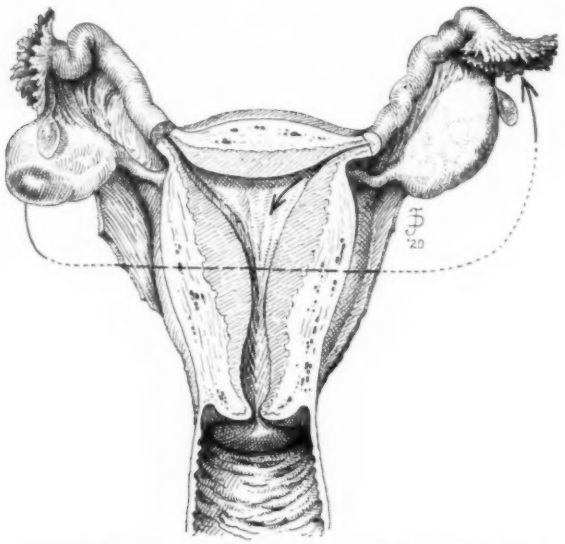

FIG. 2.—Diagram illustrating external migration of the human ovum. Four-fifths natural size.

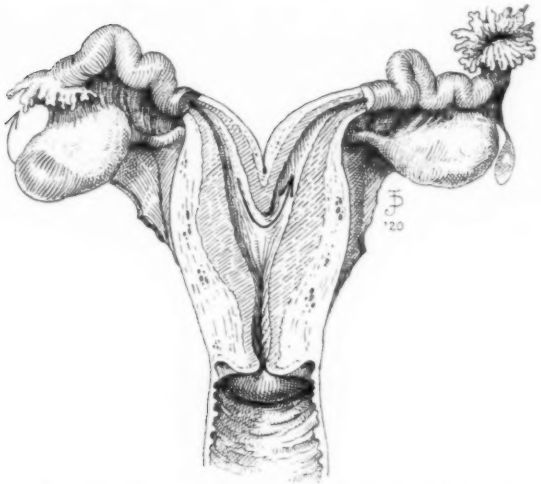

FIG. 3.—Diagram illustrating hypothetical internal migration of the human ovum. Four-fifths natural size.

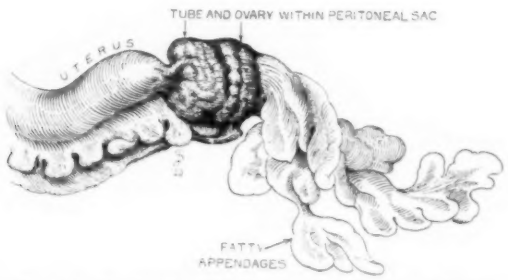

FIG. 4.—Illustrating closed ovarian capsule of Fallopian tube in the rat, which makes external migration of the ovum impossible. × 7.

ciliated lining and possibly by peristaltic movements of the Fallopian tubes, which produce currents in the films of abdominal fluid between the pelvic organs, by which ova may

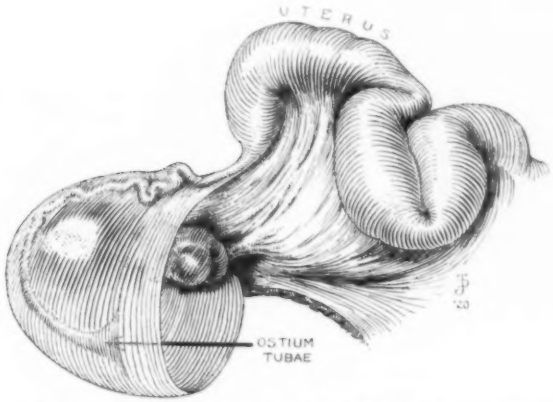

FIG. 5.—Illustrating form of the Fallopian tube of the sow, theoretically permitting migration of the ovum by either route. Two-thirds natural size.

be drawn into the open ostia. Experimental evidence of external migration has been given by Leopold (1880), who excised one tube and the opposite ovary in rabbits, and found the animals still capable of bearing young.

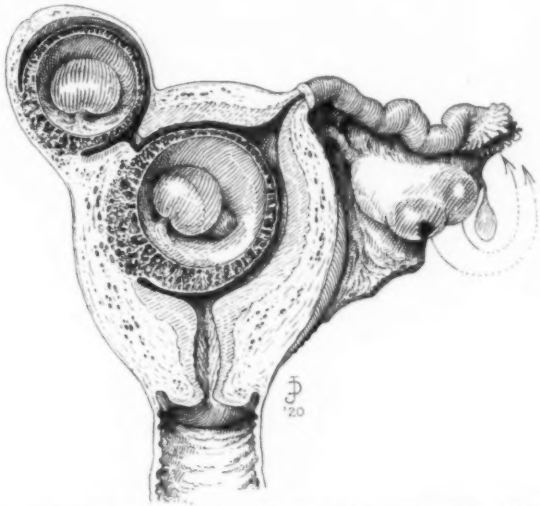

FIG. 6.—Diagram constructed from the verbal description of Andrews' case of supposed internal migration of the human ovum (see text).

With the rarest exceptions, all convincing human cases of migration of the ovum are capable of explanation by the external route. No conclusive evidence, clinical or experimental, has been found to show that internal migration occurs, and thus it has remained merely a hypothetical possibility. Andrews (1912-13), however, has recently reported a case (Fig. 6) which seems to fall into this class, since there was an interstitial pregnancy in the right side which could be excised

without opening the uterine cavity, with a normally implanted twin embryo in the uterine cavity, in a woman whose right tube and ovary were entirely absent.

Undoubtedly, however, much of the supposed evidence for migration from clinical cases has been uncritical or incomplete, so that Burckhard (1904) did not hesitate even to deny the occurrence of migration by either route, except in a few human cases in which there is a previous abnormal arrangement of the pelvic organs. Under this exception he admits some of the cases of tubal pregnancy in the contralateral tube, as described above. In those human and experimental cases in which previous excision of a tube is part of the *mise-en-scène*, he feels that the possibility of subsequently recurring patency of the stump has not been sufficiently considered; and in the study of animals with bicornate uteri and large litters, he believes errors have arisen in consequence of the failure of some of the corpora lutea to develop or to persist, or, on the other hand, because no allowance was made for the possible persistence of corpora lutea from previous ovulations. Although these objections are not all tenable, they must at least be considered in future attempts to demonstrate one or the other kind of migration of the ovum.

With respect to the pig, the present writer has direct information as to the possible causes of error suggested by Burckhard. As before pointed out (Corner 1915), there is no likelihood of confusing corpora lutea of different ovulations, owing to their rapid retrogression; while failure of corpora lutea to develop or to persist during pregnancy has never been observed in a rather large experience. Polyovular follicles undoubtedly occur and may perhaps even attain full development and discharge of their ova, but they are rare, and no experienced student of the ovary could believe them sufficiently numerous to explain away a frequency of migration amounting to one-third or more of all pregnancies. Therefore, as will be confirmed by additional evidence to be given below, in the pregnant sow the number of corpora lutea found in the ovaries probably represents with perfect accuracy the number of eggs which were discharged into the Fallopian tubes at the ovulation which gave rise to the pregnancy.

The Evidence for Internal Migration

In the writer's previous brief discussion of migration of the ovum in swine, to which reference has already been made, it was assumed that the cases were of the external variety, merely because this hypothesis had been proven more likely with regard to the human cases. Küpfer (1920) who has studied seven cases of migration in swine, makes the contrary assumption as to the route. In this guess he is correct, for the statement can now be made that after all, in the pig, external migration has not been demonstrated, but that migration of fertilized ova by the internal route is a frequent phenomenon of physiological significance.

The evidence which not only demonstrated internal migration, but also suggests some of the factors which regulate the process, has been extracted from data gathered (for another purpose) during a detailed examination of the ovaries and uteri of 545 sows. The work was done during a stay at the Station for Experimental Evolution of the Carnegie Institution of Washington, at Cold Spring Harbor, Long Island, and the writer is most grateful to the Director, Dr. C. B. Davenport, for the opportunities afforded. Further thanks are due to Messrs. Joseph Stern and Company, meat packers, of New York City, for material, and to Mr. Clyde E. Keeler for assistance.

TABLE I

Showing Numbers of Corpora Lutea in Ovaries, and of Ova in Fallopian Tubes, in 26 Consecutive Cases of Recent Ovulation in Swine

Serial number	Corpora lutea in left ovary	Corpora lutea in right ovary	Ova in left tube	Ova in right tube	Total corpora lutea	Total ova found	Ova not found
1	3	0	3	0	3	3	..
2	3	5	3	5	8	8	..
3	7	4	7	4	11	11	..
4	3	6	3	5	9	8	1
5	4	5	4	5	9	9	..
6	5	2	5	2	7	7	..
7	5	4	5	3	9	8	1
8	6	3	6	3	9	9	..
9	2	6	2	6	8	8	..
10	4	3	4	3	7	7	..
11	7	5	7	5	12	12	..
12	4	6	4	6	10	10	..
13	5	3	4	2	8	6	2
14	4	2	4	2	6	6	..
15	11	0	11	0	11	11	..
16	6	2	6	2	8	8	..
17	5	3	5	3	8	8	..
18	8	1	7	1	9	8	1
19	5	6	5	6	11	11	..
20	4	3	4	3	7	7	..
21	8	2	7	2	10	9	1
22	4	5	4	5	9	9	..
23	4	4	4	4	8	8	..
24	4	3	4	3	7	7	..
25	5	3	4	3	8	7	1
26	5	3	5	3	8	8	..
Totals	131	89	127	86	220	213	7

Twenty-six consecutive sows were selected, by the appearance of the ovaries, as having ovulated within the past three days; the ova were therefore en route through the Fallopian tubes, and were actually recovered therefrom, by a method previously described (Corner and Amsbaugh, 1917). By using great care in the procedure, and washing out each tube as often as

five times when necessary, it was found possible to collect from a given sow, with almost mathematical certainty, all the ova expected on the basis of the corpus luteum count. In all 26 sows examined, there was a total of 220 corpora lutea, against which 213 ova were regained from the oviducts, or 96 per cent of those expected (Table I).

TABLE II

SHOWING DISTRIBUTION OF EMBRYOS IN UTERUS, WHEN EQUAL NUMBERS OF OVA WERE DISCHARGED FROM EACH OVARY

Serial number	Corpora lutea in left ovary	Corpora lutea in right ovary	Embryos in left cornu	Embryos in right cornu	Result
27	4	4	4	4	
28	6	6	6	6	
29	4	4	4	4	
30	3	3	3	3	
31	4	4	4	4	
32	5	5	5	5	
33	5	5	5	5	
34	4	4	4	4	
35	4	4	4	4	No migration.
36	3	3	3	3	
37	3	3	3	3	
38	5	5	5	5	
39	3	3	3	3	
40	4	4	4	4	
41	4	4	4	4	
42	3	3	3	3	
43	3	3	3	3	
44	3	3	4	2	
45	3	3	4	2	Migration of one ovum in each case.
46	4	4	5	3	
47	7	7	8	6	

The reader will have noticed that not only practically all the discharged ova are readily discoverable, but also that the eggs in a single tube are always accounted for by the discharged follicles (corpora lutea) in the corresponding ovary. In these 26 consecutive cases, then, there was no case of external migration.

Next a similar table was made by counting the corpora lutea and the embryos of nearly 500 pregnant sows which were passing through the same abattoir. In these animals, in spite of the fact already mentioned, that a large early embryonic mortality obscures and lowers the apparent proportion of migration, still (as was found some years ago) about one-third of the sows show migration of one or more ova. If distributed, for the sake of comparison with the first series, into groups of 26, no such group contains less than five cases in which migration occurs.

These two facts, that migration in general is very common, but external migration rare or non-existent, together prove the occurrence of internal migration of the fertilized ovum of the sow.

DETERMINING FACTORS AND PROBABLE UTILITY OF INTERNAL MIGRATION OF THE OVUM

We may now venture the hypothesis that the phenomenon of internal migration has a practical utility in the pig; it is important that the individual embryos of the large litters shall each find a fair share of space in the uterine cavity. As shown by the examples in Table I, the right and left ovaries often discharge very unequal numbers of ova, which might well lead, were it not for migration, to the overcrowding of embryos in one cornu.

TABLE III

SHOWING DISTRIBUTION OF EMBRYOS IN UTERUS, WHEN THE TOTAL NUMBER OF OVA DISCHARGED WAS UNEVEN, ONE OVARY EXCEEDING THE OTHER BY ONE OVUM

Serial number	Corpora lutea in left ovary	Corpora lutea in right ovary	Embryos in left cornu	Embryos in right cornu	Result
48	5	4	5	4	
49	4	3	4	3	
50	3	4	3	4	
51	4	3	4	3	
52	4	5	4	5	
53	5	6	5	6	
54	5	4	5	4	No migration.
55	4	5	4	5	
56	3	4	3	4	
57	4	3	4	3	
58	3	4	3	4	
59	4	3	4	3	
60	3	2	3	2	
61	3	4	3	4	
62	6	5	5	6	
63	5	6	6	5	
64	4	5	5	4	
65	3	4	4	3	
66	3	2	2	3	Migration of one ovum.
67	3	4	4	3	
68	5	4	4	5	
69	3	4	4	3	
70	3	4	4	3	
71	2	3	4	1	Migration beyond balance.

This suggestion was tested by analysis of the records of the pregnant uteri, from the whole series only those cases, 113 in

number, being chosen, in which all the corpora were represented by normally implanted embryos, thus avoiding the obscuring effect of early embryonic degeneration. If migration is by rule and not by chance, then in these cases we should find: (1) that when the ovaries discharge equal numbers of ova, the number of embryos in each chamber remains equal; (2) however unequal the output of the two ovaries, the number of embryos in the uterine cornua should tend to approach equality. It will also be clear that cases which deviate from these expectations should be commonly those in which the litters are small, and further that they will be damaging to the hypothesis in proportion to the number of ova which in any one case migrate in the adverse direction.

I. In 21 cases the ovaries discharged equal numbers of eggs. By hypothesis there should have been no migration. Result: no migration in 17 cases, but in four cases there was migration of one ovum in each (Table II).

II. In 24 cases the total number of eggs discharged was uneven, one ovary exceeding the other by one egg. In this circumstance, by our hypothesis it is a toss-up whether or not one ovum shall migrate, as the balance cannot be perfectly restored. Result: no migration in 14 cases; migration of one ovum in 9 cases; migration beyond balance in one case; migration toward excess side, no case (Table III).

III. In 68 cases, the output of one ovary exceeded that of the other by two or more eggs. By hypothesis there should have been migration toward the lesser side in all cases. Result: in 21 cases perfect balance was obtained by migration; in 20 more, the total number of eggs being uneven, balance was restored to $\pm\frac{1}{2}$. In 3 cases, in all of which the discrepancy between the ovaries was great, perfect balance was not quite attained in the uterus (Cases 113-115). In 9 cases migration did not stop at an even balance; in 7 of these one ovum too many went over, in 2 cases two ova migrated beyond the balance, in no case, however, forcing more than seven embryos into the uterine chamber. In 14 cases there was no migration at all, but in all these the original imbalance was small in degree, so that the need of migration was slight. In one case there was migration of one ovum toward the excess side (Case 139, Table IV).

To sum up, the hypothetical expectation was fulfilled in 84 of 113 cases, with 29 deviations, all of which were trivial in degree; hence the supposition that the process of internal migration is under physiological regulation for useful ends seems to be justified.

The anatomical mechanism of internal migration is now open to conjecture and experiment, but there can be but little doubt that the embryos are shifted by the peristaltic action of the uterine musculature. Some such action must be postulated in any case to account for the regular spacing of the implanted embryos within the uterus; and the only novelty in the present contribution is the notion that both cornua act as one continuous tube, which must be readily capable of peristalsis in either direction. It may well be also that the peculiar form of the ungulate blastodermic vesicle, which reaches the length of 30 or more centimeters before implantation, may render it espe-

TABLE IV

SHOWING DISTRIBUTION OF EMBRYOS IN UTERUS, WHEN THE OUTPUT OF THE OVARIES WAS UNEQUAL, ONE OF THE OVARIES EXCEEDING THE OTHER BY TWO OR MORE OVA

Serial number	Corpora lutea in left ovary	Corpora lutea in right ovary	Embryos in left cornu	Embryos in right cornu	Result
72	4	6	5	5	
73	5	7	6	6	
74	6	4	5	5	
75	4	6	5	5	
76	8	0	4	4	
77	5	3	4	4	
78	6	4	5	5	
79	2	4	3	3	
80	6	4	5	5	
81	5	1	3	3	
82	8	2	5	5	Migration to exact balance.
83	2	6	4	4	
84	1	3	2	2	
85	4	2	3	3	
86	1	5	3	3	
87	8	0	4	4	
88	5	1	3	3	
89	4	2	3	3	
90	6	2	4	4	
91	3	1	2	2	
92	5	1	3	3	
93	5	2	4	3	
94	4	1	2	3	
95	3	6	5	4	
96	7	2	4	5	
97	6	3	4	5	
98	4	7	5	6	
99	6	1	4	3	
100	5	0	3	2	
101	2	5	3	4	Total number of ova uneven; balance restored to $\pm\frac{1}{2}$.
102	1	8	5	4	
103	3	6	4	5	
104	2	7	5	4	
105	1	4	3	2	
106	4	1	3	2	
107	4	1	3	2	
108	4	1	2	3	
109	2	5	3	4	
110	8	5	7	6	
111	8	1	4	5	
112	5	2	3	4	
113	11	0	8	3	Balance not fully restored.
114	7	0	5	2	
115	1	9	4	6	
116	2	8	6	4	
117	6	0	2	4	
118	4	7	7	4	
119	9	3	5	7	
120	6	2	3	5	Migration beyond balance.
121	7	4	4	7	
122	2	6	5	3	
123	4	0	1	3	
124	5	3	3	5	
125	5	3	5	3	
126	6	4	6	4	
127	5	3	5	3	
128	5	3	5	3	
129	2	4	2	4	
130	6	4	6	4	
131	4	6	4	6	No migration.
132	4	6	4	6	
133	2	5	2	5	
134	4	2	4	2	
135	3	1	3	1	
136	3	5	3	5	
137	1	4	1	4	
138	5	3	5	3	
139	6	7	5	8	Migration toward excess side.

cially suitable for transportation by the uterus. It will be of much interest to learn whether migration of the pig's ovum can be demonstrated before the tenth day, while it is still minute and spherical.

If the forgoing discussion has any bearing upon the clinical side of the question, it is that internal migration of the human ovum is still to be regarded as occasionally possible, more especially perhaps in cases of multiple gestation. Twin embryos were present in the case of Andrews, previously mentioned, which is up to the present the most satisfactory case among those interpreted as examples of this form of migration in the human.

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SERIOUS REACTIONS TO REPEATED TRANSFUSIONS IN PERNICIOUS ANEMIA

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Since the introduction of blood transfusion as a therapeutic procedure in the treatment of pernicious anemia, numerous reports have appeared upon the various phases of reactions after transfusion. Three cases are here reported, in which after a large number of transfusions, there occurred extremely severe reactions following the transfusion of apparently compatible blood. Cases I and II of this series have been briefly referred to by Sydenstricker, Mason and Rivers,[3] who concluded that transfusion is a self-limited process in pernicious anemia. In two of the cases the severity of the reaction seems to have been largely responsible for the death of the patient. It was considered inadvisable and dangerous to continue this form of therapy in the other patient, who died a short time after discharge from the hospital.

Blood matching of recipient *vs.* donor was carried out in every instance, and the donor chosen only in complete absence of microscopic agglutination or hemolysis of the donor's cells by the recipient's serum, or the recipient's cells by the donor's serum. The matching was carried out according to the method described by Sydenstricker and others.[1] A small amount of blood is drawn into a Wright pipette or test-tube and centrifuged to obtain the serum. A cell suspension is made by mixing two drops of blood in 5 c. c. of normal salt solution, which may contain 0.125 per cent sodium citrate. Coverslips are passed through 95 per cent alcohol and polished. One drop of serum and one drop of cell suspension are placed on the coverslip by means of capillary tubes, and mixed with a glass rod. The preparation is then inverted on a hollow ground slide, sealed with oil, and examined. In several instances early in the series of transfusions the incubation period was only 30 minutes. It was noted in Transfusion V of Case I that agglutination did not occur at the end of 30 minutes, but did occur at the end of 45 minutes. Consequently, later matchings were incubated for one hour or longer. In every instance in which the donor had given blood for an earlier transfusion he was rematched against the blood of the recipient before being used again, for it has been shown by McClure and Dunn [2] that a donor may be found compatible for one transfusion, but may be incompatible for a subsequent transfusion and this can be demonstrated by blood matching.

The early transfusions of the series were carried out by the Lindemann syringe-cannula method.[2] In the later transfusions the citrate method described by Lewisohn [4] was used.

This series of cases is reported chiefly to show the inadequacy of the present method of determining the compatibility of blood for transfusion, particularly in those cases in which the recipient has been the subject of a large number of earlier transfusions.

CASE I

FIRST ADMISSION

J. B. Female, *act.* 43, white, married, occupation—housewife. Medical No. 34717. *Diagnosis:* Pernicious anemia. Transfusion of blood. Reaction following blood transfusion. Admitted: September 10, 1915.

The *complaint* was weakness, shortness of breath and increasing pallor.

The family history was negative.

Past History.—The patient had scarlet fever at 6. She had had two miscarriages. During the past two years her periods had been more profuse than normal. There had been diarrhea at times.

Present Illness.—For over a year the patient had been troubled with burning on urination, a scalded and burning sensation in her mouth, and a chronic cough. For the past ten months she had suffered from lightheadedness, and for the past two months roaring in her ears. She had noticed a yellow coloration of the skin, numbness and tingling in her fingers and toes, palpitation and dyspnœa on exertion, œdema of her feet recently, and dimness of vision at times.

The physical examination showed a general pallor with sallowness of the complexion and an icteric tint to the sclerotics and skin, striking pallor of the mucous membranes, slight diffuse enlargement of the thyroid, bleeding from the gums, and retinal hemorrhages. The relative cardiac dulness measured 14 cm. by 3.5 cm., and there was a blowing systolic murmur at the apex. The liver extended one finger's breadth below the costal margin on inspiration, and the spleen was palpable at the costal margin. There was slight pitting œdema of the ankles. The blood pressure was 140/95. The patient showed an almost constant elevation of temperature from 100° to 102° F.

Laboratory.—Hb. (Sahli) = 27%. R. B. C. = 1,136,000. W. B. C. = 3,560. The stained smear showed a typical picture as demonstrated in the charts. Gastric analysis showed a hydrochloric acid deficit of 8%, and a combined acid of 2%. The Wa. R. was negative. The urine showed a trace of albumin and a few W. B. C.

TRANSFUSIONS

I. Eight hundred cubic centimeters of matched whole blood given during 30 minutes by the Lindemann method. Upon returning to the ward the patient experienced a generalized itching sensation over her body; the skin was somewhat flushed and an urticarial eruption developed. She vomited once. There was slight temperature elevation. Donor, H. E. B., husband.

II. Nine hundred cubic centimeters of matched whole blood given during 30 minutes. Lindemann method. No reaction. Donor, J. A. D.

III. Nine hundred cubic centimeters of matched whole blood. Lindemann method. Upon returning to the ward the patient complained of itching all over and vomited once. No other reaction. Donor, H. W. D.

IV. Nine hundred cubic centimeters of matched whole blood. Lindemann method. No reaction. Donor, M. E. B.

V. The donor's and recipient's blood had been incubated and read at the end of 30 minutes for matching; there was no agglutination or hemolysis. Twenty cubic centimeters of blood were withdrawn from the donor and injected into the vein of the recipient; the latter had been feeling perfectly well. Almost instantly the patient's face became flushed and she complained of feeling badly and aching all over, and especially of pain in her arms and back. Her respirations became more rapid and there was slight cyanosis; she complained of a choking sensation and coughed several times. No more blood was injected. The symptoms became slowly more marked and the patient attempted to vomit several times. Transfusion was abandoned. Upon returning to the ward the patient had a severe chill lasting 40 minutes and a transient temperature elevation to 102° F. The pulse was weak and variable. Urine voided five hours later gave a positive test for Hb. The blood of the recipient and of the donor were rematched; at the end of 30 minutes the preparations were negative, but at the end of 45 minutes, in thick preparations, there was marked agglutination of the recipient's red blood cells by the serum of the donor. Thin preparations were negative at the end of one hour. Four hours following this reaction the patient felt perfectly well. Donor C. W. D.

VI. Nine hundred cubic centimeters of matched whole blood. Lindemann method. No reaction. Donor, husband.

X-30-15. The patient was discharged. Hb = 62%. R. B. C. = 4,000,000.

SECOND ADMISSION

Medical No. 35134. *Diagnosis:* Pernicious anemia. Transfusion of blood. Admitted: December 6, 1915. The *complaint* was weakness.

During the previous three weeks the patient had been troubled with palpitation and pounding in her ears, dyspnœa on exertion and edema of the ankles at night. She entered the hospital for an examination of her blood.

The *physical examination* was as upon the previous admission. In addition, there were fresh retinal hemorrhages. Her temperature ranged from 99.8° to 100.6° F. up to the time of the first transfusion, after which it remained normal. Blood: Hb. (Sahli) = 29%. R. B. C. = 1,148,000. W. B. C. = 4,000. Resistance of R. B. C. to hypotonic salt solution (fragility test): Hemolysis began at 0.40% and was complete at 0.25%. The urine showed a very faint trace of albumin, and a positive test for urobilin.

TRANSFUSIONS

VII. Seven hundred and eighty-eight cubic centimeters of matched whole blood. Lindemann method. The patient became restless, but suffered no reaction. Donor, J. A. D., brother.

VIII. Nine hundred and two cubic centimeters of matched whole blood. Lindemann method. The patient complained that her eyelids felt swollen, and of slight itching in the palms of her hands. No other reaction. Donor, C. W. D.

IX. Eight hundred cubic centimeters of matched whole blood. Lindemann method. No reaction. Donor, husband.

XII-21-15. The patient was transferred to the Surgical Department for splenectomy. Hb. = 60%. R. B. C. = 3,432,000.

SURGICAL ADMISSION

Surgical No. 38909. *Diagnosis:* Pernicious anemia. Admitted December 21, 1915.

XII-21-15. Splenectomy was performed. There was a slight oozing of blood from the operative wound which ceased with a transfusion of 286 cubic centimeters of blood.

TRANSFUSIONS

X. Two hundred and eighty-six cubic centimeters of matched whole blood. Lindemann method. No reaction. Donors, A. D., brother, and B., husband.

XI. Five hundred and twenty cubic centimeters of matched whole blood. Lindemann method. No immediate reaction. Upon returning to the ward the patient complained of itching of her back which showed an urticarial eruption. Her pulse went to 140 per minute and her respirations to 40. There was a chill, lasting about 30 minutes, and the patient became quite cyanotic. There was a transient elevation of temperature to 101.5°. The reaction lasted one hour. Donor, S. I. L.

XII. Five hundred and fifty cubic centimeters of matched whole blood. Lindemann method. No reaction. Donor, not stated.

XIII. Six hundred and sixty cubic centimeters of matched whole blood. Lindemann method. No reaction. Donor, husband.

XIV. Two hundred and seventy cubic centimeters of matched whole blood. Lindemann method. No reaction. Donor, W.

II-15-16. There was an uneventful recovery from splenectomy. The patient was discharged. Hb. = 82%.

THIRD ADMISSION

Medical No. 36344. *Diagnosis:* Pernicious anemia. Transfusion of blood. Admitted: August 2, 1916.

The patient had been in fair condition while at home; she had rested a great deal and spent half of each day in bed. She had recently been growing gradually weaker, and there had been edema of the ankles when she was up out of bed.

The *physical examination* was the same as upon previous admissions. In addition, there was slight edema of the ankles, and a splenectomy scar in the left abdomen. There was a constant elevation of temperature ranging from 100° to 102°. Hb. = 24%. R. B. C. = 1,238,000. W. B. C. = 9,250. The urine showed a faint trace of albumin and a positive guaiac test for hemoglobin.

TRANSFUSIONS

XV. Three hundred and fifty cubic centimeters of matched whole blood. Citrate method. The blood was given slowly during one hour. Twenty minutes after the procedure, the patient had a severe shaking chill, the temperature rising rapidly to 106° F., and falling gradually. There was no hemoglobinuria on repeated examinations. This transfusion was held very badly and the hemoglobin and red blood cell count continued to drop. Donor, B., husband.

XVI. Five hundred and fifty cubic centimeters of matched whole blood. Citrate method. During this operation a great deal of trouble was experienced from the blood clotting in the needle; the clotting seemed to take place immediately upon contact between the donor's and the recipient's blood. This difficulty was overcome by adding twenty-five cubic centimeters of sodium citrate. There was an immediate severe reaction with a shaking chill lasting about twenty minutes, an elevation of temperature to 106.6° F. and nausea. The temperature fell gradually to its former level. There was a marked hemoglobinuria which persisted until the time of death. There had been no untoward symptoms after the injection of the first twenty cubic centimeters of blood. Donor, D., brother.

VIII-14-16. The patient had grown progressively weaker, and showed no improvement in the blood picture. Inasmuch as better results had been obtained on previous admissions with the Lindemann method of transfusion, it was decided to make use of this procedure.

XVII. Seven hundred cubic centimeters of matched whole blood. Lindemann method. Twenty cubic centimeters of blood were given and after a wait of ten minutes there had been no reaction. The remainder of the blood was given in about forty minutes. The patient had no reaction while on the table, but on the way to the ward she developed a severe shaking chill, lasting about thirty minutes, with an elevation of temperature to 104° F. This was accompanied by marked cyanosis, without any demonstrable signs of cardiac dilatation, dyspnœa, pain in the back, and marked general discomfort. Subjectively, this was the severest reaction which the patient had had. There was marked hemoglobinuria; the urine was almost black. Seven hours later the patient was a little more comfortable but still in a critical condition with a temperature of 103.6° F. and a pulse of 160, weak in quality. Donor, T. A. L.

VIII-15-16. The patient had been irrational all day with a temperature of 102.4° F. and a pulse of 130, of poor quality. Strophanthin, Murphy drip per rectum, and subcutaneous infusion of normal salt solution produced no improvement; she had to be catheterized, and 300 cubic centimeters of black urine were obtained, showing a strongly positive guaiac reaction, but no casts or red blood cells.

VIII-17-16. There was still a marked hemoglobinuria in catheterized specimens of urine. The patient died at 6.45 a. m.

MACROSCOPIC MATCHINGS WITH VARIOUS DILUTIONS OF DONOR'S AND RECIPIENT'S R. B. C. AND SERA

	c. c.	c. c.	c. c.	c. c.	c. c.	c. c.	c. c.	
Recipient's serum	1/4	1/4	1/4	1/4	1/4	1/4	1/4	No agglutination
Donor B., R. B. C.—50%	1/4	1/8	1/16	1/32	1/64	1/128	1/256	or hemolysis.
Recipient's serum	1/4	1/4	1/4	1/4	1/4	1/4	1/4	No agglutination
Donor D., R. B. C.—50%	1/4	1/8	1/16	1/32	1/64	1/128	1/256	or hemolysis.
Recipient's serum	1/4	1/8	1/16	1/32	1/64	1/128		No agglutination
Donor B., R. B. C.—10%	1/4	1/4	1/4	1/4	1/4	1/4		or hemolysis.
Recipient's serum	1/4	1/8	1/16	1/32	1/64	1/128		No agglutination
Donor D., R. B. C.—10%	1/4	1/4	1/4	1/4	1/4	1/4		or hemolysis.

CASE I

Date	Hb.	R. B. C.	W. B. C.	P. M. N.	P. M. E.	P. M. B.	S. M.	L. M.	Tr.	Myelocytes	Anisocytosis	Poikilocytosis	Punctate basophilia	Diffuse basophilia	Nucleated R. B. C.	Macrocytes	Microcytes	Platelets	Vital staining R. B. C.	Transfusions
IX-10-15	27%	1,136,000	3,560	66.0	.5	.5	27.5	3.0	1.0	1.5	+	+	—	—	0	+	+	..	..	.....
IX-24-15	20	680,000	..	....	..	..	....	....	..	..	..	..	..	..	..	..	..	..	..	9-25-15 800 c. c.
IX-29-15	35	1,664,000	2,160	....	..	..	....	....	..	..	..	..	..	..	..	..	..	..	..	9-30-15 900 c. c.
X- 9-15	55	2,240,000	3,280	52.5	.5	0	42.0	3.5	0	1.5	..	..	..	..	1.0	..	..	..	..	10- 9-.5 900 c. c.
X-15-15	50	3,360,000	....	....	..	..	....	....	..	..	..	..	..	..	..	..	..	..	..	10-16-15 900 c. c.
X-18-15	55	4,170,000	....	....	..	..	....	....	..	..	..	..	..	..	..	..	..	..	..	10-23-15 20 c. c.
X-24-15	52	2,672,000	....	....	..	..	....	....	..	..	..	..	..	..	..	..	..	..	..	10-30-15 900 c. c.
X-31-15	62	4,000,000	....	70.0	1.6	.4	20.0	3.6	1.6	2.8	0	..	..	..	..	..	..	..	..	.....
XII- 6-15	29	1,148,000	4,000	56.5	.5	0	41.0	1.5	.5	0	+	+	+	+	0	+	+	..	..	Second admission. 12-10 15 788 c. c.
XII-14-15	42	2,450,000	3,100	....	..	..	....	....	..	..	..	..	..	..	..	..	..	..	..	12-14-15 902 c. c.
XII-17-15	52	2,968,000	3,280	....	..	..	....	....	..	..	..	..	..	..	..	..	..	..	..	12-18-15 800 c. c.
XII-19-15	60	3,432,000	....	....	..	..	....	....	..	..	..	..	..	..	..	..	..	..	..	12-21-15 286 c. c. Splenectomy.
XII-22-15	48	3,000,000	7,000	....	..	..	....	....	..	..	..	..	..	..	..	..	..	..	..	12-30-15 520 c. c.
I- 7-16	60	3,024,000	4,760	33.0	0	0	54.5	7.0	3.0	2.5	..	..	..	+	7	..	..	..	..	1-22-16 550 c. c.
II-11-16	74	3,208,000	6,080	53.5	2	.5	23.5	13.5	4.0	0	..	..	..	..	1.0	..	..	..	..	2-12-16 680 c. c. 2-13-16 270 c. c.
II-15-16	82	.....	....	....	..	..	....	....	..	..	..	..	..	..	..	..	..	..	..	.....
VIII -2-16	24	1,238,000	9,250	....	..	..	....	....	..	..	..	..	..	..	..	..	..	..	..	Third admission. 8- 3-16 350 c. c.
VIII- 4-16	30	1,560,000	....	43.5	1.0	.5	52.5	.5	.5	1.5	+++	+++	+	+	57	..	..	..	..	.....
VIII- 7-16	28	1,112 000	....	....	..	..	....	....	..	..	..	..	..	..	..	..	..	..	..	8- 9-16 550 c. c
VIII-12-16	26	1,544,000	....	....	..	..	....	....	..	..	..	..	..	..	..	..	..	..	..	.....
VIII-15-16	25	1,048,000	10,400	....	..	..	....	....	..	..	..	..	..	..	..	..	..	..	..	8-15-16 700 c. c.
VIII-16-16	24	.....	19,400	60.0	..	..	....	....	..	..	..	..	..	..	..	..	..	..	..	.....

Analysis.—This patient (Case I) had three admissions to the hospital during a period of 11 months, and received a little more than 10¾ liters of blood in 17 transfusions. Eight times during this series she experienced reactions of varying degrees of severity, showing a marked hemoglobinuria on three occasions. Transfusion V gave one of the most severe reactions accompanied by hemoglobinuria, although only 20 c. c. of blood were injected. The same donor seems to have been used for the eighth transfusion, which was followed by no reaction except pruritus and discomfort about the eyelids. The patient's husband acted as donor six times, giving a total of 3,620 c. c. of blood, with one mild reaction, after Transfusion I, shown by urticaria and pruritus, and with one severe reaction, after Transfusion XV, shown by a severe shaking chill and an elevation of temperature to 106° F., but no hemoglobinuria; on four occasions his blood produced no reaction of any sort. Splenectomy gave no permanent benefit. After the reactions to Transfusions XV and XVI macroscopic matchings of the recipient's serum against the donor's cells were carried out with varying dilutions of serum and cell suspension; they were all negative for agglutination or hemolysis.

CASE II

First Admission

H. A. P. Male. *Aet.* 62. White, widowed; occupation—oiler of machinery. Medical No. 35335. *Diagnosis:* Pernicious anemia. Admitted: January 3, 1916.

The *complaint* was weakness and lack of blood.

Family History.—One brother had died of cancer of the rectum; one sister had died of tuberculosis. Otherwise, negative.

Past History.—The patient's general health had been good. He had had recurrent attacks of malaria from 10 to 50 years of age; had always worked hard, 11 to 13 hours daily, exposed to high temperatures. Otherwise negative.

Present Illness.—The symptoms were of one year's duration. He had first noticed frequency of urination; later, weakness in his knees, and then the entire body, which had become progressively worse. The weakness was accompanied by shortness of breath. During the three weeks before admission there had been precordial pain on exertion, and he had become too weak to work. He had suffered from anorexia and constipation and had vomited on one occasion. There was early loss of sexual power. He had lost 37 pounds in weight since the onset of his illness.

The *physical examination* revealed dyspnœa on slight exertion, a lemon tint of the skin, a flabby musculature, and evidence of loss of weight, but with a still thick layer of subcutaneous fat. The right pupil was larger than the left. There was marked oral sepsis, and the tongue showed papillary atrophy. A faint systolic murmur was heard at the apex of the heart. The blood pressure was 118/60. There was slight edema of the ankles. The fundi showed numerous retinal hemorrhages. There was a constant elevation of temperature ranging from 99° to 101° F.

Laboratory.—Blood: Hemoglobin (Sahli) = 26%. R. B. C. = 936,000. W. B. C. = 5,440. Gastric analysis showed no free acid. The urine showed albumin and granular casts. The Wa. R. was negative.

TRANSFUSIONS

I. Two hundred cubic centimeters of whole blood. Lindemann method. The patient had a severe chill with signs of collapse and an elevation of temperature to 102.8° F. There was no hemoglobinuria. Donor, E. M. P.

II. Three hundred cubic centimeters of matched whole blood. Lindemann method. No reaction. Donor, A. P.

III. Six hundred and eighty-two cubic centimeters of matched whole blood. Lindemann method. No reaction except an elevation of temperature to 101° F. Donor, L. P.

IV. Six hundred and forty cubic centimeters of matched whole blood. Lindemann method. No reaction. Donor, C. N. P.

V. Six hundred and thirty-eight cubic centimeters of matched whole blood. Lindemann method. The patient felt chilly after the transfusion, but there was no rise in temperature. Two urticarial wheals developed, and the patient vomited once. No other reaction. Donor, H.

VI. Six hundred and sixty cubic centimeters of matched whole blood. Lindemann method. The patient felt chilly and his temperature rose to 101.6° F. No other reaction. Donor, W. B. P.

11-8-16. Hb. = 65%. R. B. C. = 4,680,000. W. B. C. = 1,400.

11-12-16. Transferred to the Surgical Clinic for splenectomy.

Surgical No. 39006. 11-12-16. Splenectomy was performed.

VII. Four hundred and forty cubic centimeters of matched whole blood. Lindemann method. No reaction. Donor, Y.

VIII. Three hundred and fifty cubic centimeters of matched whole blood. Lindemann method. No reaction. Donor, E. P.

11-28-16. Hb. = 80%. R. B. C. = 3,170,000. W. B. C. = 7,200.

11-29-16. The patient was transferred to the Medical Service. There was an uneventful recovery from the operation.

Medical No. 35677. IX. Five hundred cubic centimeters of matched whole blood. Lindemann method. Several hours later the patient complained of a slight chill and his temperature rose to 102° F. Many large urticarial wheals appeared over the entire body, but there were no other symptoms and no hemoglobinuria. Donor, W. E. K.

X. Four hundred and fifty cubic centimeters of matched whole blood. Lindemann method. No reaction. Donor, P.

XI. Four hundred and fifty cubic centimeters of matched whole blood. Lindemann method. No reaction. Donor, brother, who had given blood once previously.

IV-19-16. The patient was discharged. Hb. = 81%. R. B. C. = 3,170,000. W. B. C. = 2,800.

Second Admission

Medical No. 36290. *Diagnosis:* Pernicious anemia; combined sclerosis. Admitted, 6-22-1916.

After leaving the hospital the patient gained 27 pounds in weight. There had been shortness of breath on exertion, palpitation, and roaring in the ears, difficulty in holding his urine if the bladder was full, frequency, and nycturia, 3 to 4 times a night. He had become very ataxic and had to use a cane in walking, and there was marked parasthesia of the feet and legs, extending as high as the umbilicus at times, and slight parasthesia of the hands and forearms.

The *physical examination* was the same as upon previous admission. In addition, there was weakness of the leg muscles, marked ataxia, a positive Romberg, loss of muscle sense in the toes, and the knee-kicks and ankle-jerks could not be obtained.

Hb. = 26%. R. B. C. = 1,136,000. W. B. C. = 7,240.

TRANSFUSIONS

XII. Five hundred cubic centimeters of matched whole blood. Citrate method. No reaction. Donor, L. C. P.

XIII. Five hundred cubic centimeters of matched whole blood. Citrate method. No reaction. Donor, C. P.

XIV. Three hundred and fifty cubic centimeters of matched whole blood. Citrate method. There was an immediate reaction with a severe shaking chill lasting 15 minutes, and a transient rise of temperature to 104° F. Nausea and vomiting occurred, and a wheezing respiration. There was no hemoglobinuria. Donor, J. P. Five hours later the patient felt fine.

XV. Four hundred cubic centimeters of matched whole blood. Citrate method. No reaction. Donor, P. This donor had been used twice previously.

XVI. Five hundred and fifty cubic centimeters of matched whole blood. Citrate method. There was a slight chill and an elevation of temperature to 101° F., but no other symptoms. Donor, H.

XVII. Five hundred and fifty cubic centimeters of matched whole blood. Citrate method. No reaction. Donor, P.

VIII-9-16. The patient was discharged.

Hb. = 60%. R. B. C. = 3,500,000. W. B. C. = 3,460.

THIRD ADMISSION

Medical No. 36839. *Diagnosis:* Pernicious anemia; combined sclerosis. Admitted: November 11, 1916.

Complaint the same as upon previous admission. There were no new complaints, but the patient felt somewhat weaker.

The *physical examination* was the same as upon the previous admission and in addition there was slight ataxia of the hands.

Hb. = 24%. R. B. C. = 1,296,000. W. B. C. = 9,600.

TRANSFUSIONS

XVIII. One hundred and fifty cubic centimeters of matched whole blood. Citrate method. There was no reaction except a slight rise in temperature. Donor, son.

XIX. One hundred and twenty cubic centimeters of matched whole blood. Citrate method. There was a very severe reaction with profuse sweating, nausea, and vomiting, and an elevation of temperature to 101.8° F. The patient became very dull and irritable, and his pulse became rapid and of poor quality. His condition was critical for several hours. There was no hemoglobinuria. Donor, son.

XX. One hundred and fifty cubic centimeters of matched whole blood. Citrate method. There was a sharp reaction 45 minutes later with a chill, nausea, and vomiting, and an elevation of temperature to 101.8° F. There was no hemoglobinuria. Donor, brother.

XII-6-16. Further transfusion was abandoned as being too dangerous. The patient was discharged.

Hb. = 18%. R. B. C. = 1,141,000.

XII-18-16. The patient died at home.

Analysis.—This patient (Case II) had three admissions to the hospital in a period of two years, and received a total of a little more than eight and one-half liters of blood in 20 transfusions. He suffered nine reactions of varying degrees of severity. On no occasion was hemoglobinuria demonstrable. During the third admission the patient's son acted as the donor for small transfusions on two occasions; from the first transfusion there was practically no reaction, while after the second reaction the recipient's condition was critical. Donor, W. B. P., was used three times; the use of his blood was followed once by chilly sensations and a slight elevation of temperature, and twice it produced absolutely no reaction. Splenectomy produced no permanent improvement in the patient's condition.

CASE III

FIRST ADMISSION

D. W. Female, *act.* 45, white, single, occupation—none. Medical No. 38864. Admitted: July 21, 1917. *Diagnosis:* Pernicious anemia, oral sepsis, rectal polyp.

The *complaint* was anemia.

The *family history* was negative.

CASE II

Date	Hb.	R. B. C.	W. B. C.	P. M. N.	P. M. E.	P. M. B.	S. M.	L. M.	Tr.	Myeloeytes	Anisocytosis	Poikilocytosis	Punctate basophilia	Diffuse basophilia	Nucleated R. B. C.	Macrocytes	Microcytes	Platelets	Vital staining R. B. C.	Transfusions
I- 3-16	26%	936,000	5,440	50.	.4	.4	28.8	2.8	.8	13.6?	++++	++	0	+++	+	—	—	—	—	1-11-16 200 c. c.
I-20-16	—	—	3,860	36.	.4	1.6	38.8	19.6	2.0	.0	++	++	—	++	10	....	....	.....	..	1-21-16 300 c. c.
I-22-16	26	1,448,000	....	..	..	..	..	..	..	..	....	....	..	..	..	....	....	.....	..	1-24-16 682 c. c.
I-25-16	36	2,352,000	....	..	..	..	..	..	..	..	....	....	..	..	..	....	....	.....	..	1-26-16 640 c. c.
I-30-16	50	2,416,000	1,440	54.8	1.2	.4	26.8	14.0	.4	.4	++++	++++	..	+	4	....	....	.....	..	2- 2-16 638 c. c.
II- 7-16	54	3,040,000	—	48.0	.8	.0	34.4	14.4	1.6	.8	++	+	—	—	6	....	....	.....	..	2- 7-16 660 c. c.
II- 8-16	65	4,680,000	1,400	..	..	..	..	..	..	..	....	....	..	..	..	....	....	.....	..	2-12-16 Splenectomy
II-14-16	47	2,376,000	4,800	72.8	2.4	.4	18.0	2.8	2.4	..	+++	+++	..	..	0	....	....	.....	..	2-19-16 440 c. c.
II-21-16	63	2,726,000	1,300	54.4	1.3	2.0	26.6	4.6	4.6	.0	++	+	..	+	7	....	....	.....	..	2-26-16 350 c. c.
II-28-16	80	3,170,000	7,200	..	..	..	..	..	..	..	....	....	..	..	..	....	....	.....	..	3- 6-16 500 c. c.
III- 7-16	76	3,824,000	6,200	80.2	1.2	1.2	12.4	2.8	1.2	.0	++	+	0	0	2	....	....	.....	..	3-13-16 450 c. c.
IV- 2-16	79	3,000,000	3,160	41.6	1.2	.4	48.8	9.2	1.2	.4	+++	++	0	0	4	....	....	Very few.	..	4- 5-16 450 c. c.
IV-19-16	81	3,128,000	2,840	32.0	2.0	.4	60.0	3.6	.4	..	++++	+	0	0	4	....	....	Very few.	..	Second admission.
VI-22-16	26	1,136,000	7,240	24.0	2.0	1.0	57.0	8.0	4.0	4.0	++++	+	+	+	216	++++	++++	Decr'd.	..	6-28-16 500 c. c.
VI-29-16	30	1,450,000	1,760	30.0	1.0	1.0	56.0	2.0	1.0	.0	+++	+++	+++	+++	76	....	....	.....	..	7- 4-16 500 c. c.
VII- 5-16	38	2,152,000	3,520	..	..	..	..	..	..	..	....	....	..	..	..	....	....	.....	..	7- 6-16 350 c. c.
VII- 7-16	45	2,480,000	—	40.0	.0	.0	34.0	3.0	1.0	5.0	....	....	+	+	16	+	....	Decr'd.	..	7-15-16 400 c. c.
VII-16-16	52	3,240,000	—	..	..	..	..	..	..	..	....	....	..	..	..	....	....	.....	..	7-22-16 550 c. c.
VIII- 3-16	50	2,696,000	....	..	..	..	..	..	..	..	....	....	..	..	..	....	....	.....	..	8- 5-16 550 c. c.
VIII- 9-16	60	3,500,000	....	..	..	..	..	..	..	..	....	....	..	..	..	....	....	.....	..	Third admission.
XI-12-16	24	1,296,000	4,120	44.0	2.0	1.0	4.0	38.0	2.0	9.0	++	++	++	++	133	....	....	Many.	..	11-14-16 150 c. c.
XI-24-16	20	1,420,000	3,444	20.0	6.0	1.0	7.0	63.0	1.0	2.0	+	+	+	+	+	....	....	.....	..	11-15-16 120 c. c.
XII- 4-16	18	1,040,000	5,000	53.0	3.0	1.0	8.0	29.0	4.0	1.0	+	+	+	+	++	....	....	.....	..	12- 3-16 150 c. c.

Past History.—Her general health had been good. There had been intermittent attacks of malaria for several years which finally cleared up with treatment. There had been slight bleeding from hemorrhoids, and she had had nycturia, sometimes once a night. She had had an acute attack of cystitis several years previously, which had cleared up with treatment. Otherwise negative.

Present Illness.—In February, 1917, the patient noticed gradually increasing weakness, and later suffered with pounding of her heart accompanied by asthenia. She had had occasional attacks of vomiting, productive of a large quantity of green fluid; later these vomiting attacks had become very frequent. In April the patient was told that she had anemia and that her hemoglobin was 40%. There had been no diarrhea, but the stools had been more fluid than normal. The patient noticed that her face was pale and that she had a lemon yellow tint to the skin of her body.

Physical Examination.—The general appearance was typical of a severe grade of pernicious anemia. There was an icteric tint to the skin and conjunctivæ. The general nutrition was excellent. There was a number of suspicious teeth and slight gingivitis. There was a soft systolic murmur at the cardiac apex.

During the first two weeks the patient ran an irregular temperature, reaching 100.5° F. almost every day, after which it remained normal with a few exceptions.

Laboratory.—Hb. (Sahli) = 10%. R. B. C. = 980,000. W. B. C. = 3,640. The stained smears showed a typical picture as shown by the chart. The urine showed a trace of albumin and some hyaline casts. The B. P. was 145/82. Her blood group was Group IV. An orthopædic consultant reported slight pronation of the left foot, apparently the result of disuse. A proctoscopic examination revealed several large external hemorrhoids and a pedunculated polyp, which was removed. Following a dental examination five teeth were extracted and the sockets curetted. A gastro-intestinal series of X-rays were made with a normal report. The Wa. R. was negative.

TRANSFUSIONS

I. Four hundred and twenty-five cubic centimeters of matched whole blood. Lindemann method. There was a slight chill, and an elevation of temperature to 103.8° F. The patient was restless and nauseated. Donor, F.

II. Five hundred cubic centimeters of matched whole blood. Citrate method. A chill occurred during the operation, and elevation of temperature to 102° F. Donor, Ct.

III. Five hundred cubic centimeters of matched whole blood. Citrate method. There was no reaction except slight discomfort. Donor, Cl.

IV. Five hundred cubic centimeters of matched whole blood. Citrate method. There was a rather marked reaction with an elevation of temperature to 102° F., and the patient was generally uncomfortable. Donor, not stated.

V. Four hundred cubic centimeters of matched whole blood. Citrate method. No reaction. Donor, H. The urine showed a positive test for urobilin after this transfusion.

VI. Four hundred cubic centimeters of matched whole blood. Citrate method. No reaction. Donor, H. (same as for previous transfusion).

XII-20-17. Discharged.

Hb. = 70%. R. B. C. = 3,460,000.

SECOND ADMISSION

Medical No. 39120. Admitted January 4, 1918. *Diagnosis:* Pernicious anemia.

The patient returned to continue the treatment. She was in excellent condition. Hb. = 70%. R. B. C. = 3,460,000.

TRANSFUSIONS

VII. One thousand one hundred and fifty cubic centimeters of matched whole blood. Citrate method. No reaction. Donors, Cs. and Cl. (The bloods of the donors were matched against each other, as well as against the blood of the patient.)

VIII. One thousand cubic centimeters of matched whole blood. Citrate method. No reaction. Donors, A and Cr.

II-16-18. Discharged.

Hb. = 71%. R. B. C. = 3,500,000. W. B. C. = 6,100.

THIRD ADMISSION

Medical No. 39836. Admitted May 18, 1918. *Diagnosis:* Pernicious anemia.

Present Illness.—Since leaving the hospital, the patient had led a fairly active life. She had felt very well until one month before admission, when she began to notice that the least effort was tiring. There was slight vertigo on turning her head.

Hb. = 74%. R. B. C. = 3,000,000.

The *physical examination* was the same as upon previous admissions, but in addition there was slight edema of the ankles.

A gastric analysis showed a hydrochloric acid deficit of 7% and a total acidity of 5%.

TRANSFUSION

IX. Seven hundred cubic centimeters of matched whole blood. Citrate method. No reaction. Donor, Cs.

VI-19-18. The patient was discharged. Hb. = 85%. R. B. C. = 2,700,000. W. B. C. = 5,160.

FOURTH ADMISSION

Medical No. 40847. Admitted November 14, 1918. *Diagnosis:* Pernicious anemia. Oral sepsis. Fascicular myelitis.

The *complaint* was of numbness in both legs.

Present Illness.—About the first of August, 1918, the patient noticed numbness in the toes of her left foot, present night and day. This sensation later extended up the right foot and the calves of the legs, and the lower part of the abdomen did not feel natural. About two weeks after the onset of this complaint, the patient voided more frequently than usual and experienced some difficulty in holding her urine.

The *physical examination* was the same as upon previous admissions. In addition, the knee-kicks and ankle-jerks were hyperactive and the sense of touch was somewhat impaired over the lower extremities.

Hb. = 75%. R. B. C. = 3,056,000. W. B. C. = 11,800. The urine gave a negative test for urobilin. Following a dental consultation, one tooth was extracted, the socket curetted, and the gingivitis was treated.

TRANSFUSIONS

XI. Four hundred and fifty cubic centimeters of matched whole blood. Citrate method. No reaction. Donor, Hl.

XII. Five hundred cubic centimeters of matched whole blood. Citrate method. No reaction. Donor, Hs.

XI-26-18. Discharged. Vitally staining R. B. C. = 0.8%. Hb. = 100%. R. B. C. = 4,008,000. W. B. C. = 7,700.

FIFTH ADMISSION

Medical No. 42333. Admitted June 5, 1919. *Diagnosis:* Pernicious anemia. Achylia gastrica. Combined sclerosis.

From the time of discharge until six weeks before admission the patient remained in good condition. She maintained a hemoglobin of 90% or higher. About six weeks ago she began to feel weak and her Hb. was 80%. One week ago the hemoglobin examination was 70% and the R. B. C. count below three millions. There has been no improvement in the condition of her legs, the numbness extending a short distance above the knees.

The *physical examination* was the same as upon previous admissions.

Hb. = 45%. R. B. C. = 1,856,000. W. B. C. = 51,000. Vitally staining R. B. C. = 0.1%.

TRANSFUSIONS

XIII. Five hundred cubic centimeters of matched whole blood. Citrate method. During the transfusion an urticarial wheal was noted on the patient's left arm. About one hour later the patient became restless, vomited, and there was an elevation of temperature to 104° F. A specimen of urine voided seven hours later gave a positive test for Hb. No red blood cells were seen in the specimen. The temperature remained elevated on the following day, and she did not void, but had to be catheterized. On the following day (second), the patient was still quite drowsy. The skin and scleræ were more icteric, and numerous small petechiæ had appeared over the body. The urine showed no abnormal blood pigments. There developed marked herpes labialis, stomatitis and glossitis. Donor, L. E. W. Group IV.

VI-13-19. The patient was still mentally confused.

XIV. Four hundred and fifty cubic centimeters of matched whole blood. Citrate method. The patient began to feel chilly and to shake toward the end of the procedure, and the last 100 cubic centimeters of blood were not run in. The temperature rose to 101.4° F., but was down on the following morning. Donor, H. F. Group IV. Several other Group IV donors were tested at the same time. There was no agglutination with any of them, but in all except the donor used, there was hemolysis of the donor's cells by the patient's serum. This fact is interesting in view of the statement by Moss[5] that the serum of any one group will not agglutinate or hemolyze the corpuscles of other members of the same group, but will agglutinate and may hemolyze the corpuscles of any other group except those of Group IV.

VIII-28-19. The patient was discharged. Hb. = 85%. R. B. C. = 2,400,000. W. B. C. = 10,000.

SIXTH ADMISSION

Medical No. 43605. Admitted March 5, 1920. *Diagnosis:* Pernicious anemia. Combined sclerosis. Chronic cystitis. Achylia gastrica. Stokes-Adams syndrome. Obesity. The patient had felt fairly well since her last admission. She had had considerable difficulty in walking and only did so with support or the aid of a cane. She stood with a broad base and there was some tendency to swaying. This condition had been growing gradually worse. She had had electrical treatment with "violet rays" along her spine without improvement. She complained of a marked feeling of discomfort in both lower extremities, and there had been incontinence of urine at times. The last time the hemoglobin determination was made at her home it was reported as 80%.

The *physical examination* was the same as upon previous admissions. In addition, the knee-kicks and ankle-jerks were strongly hyperactive, and there was a sustained ankle clonus on the left, and a fairly well sustained clonus on the right. There was a patellar clonus on both sides. Plantar stimulation gave dorsal flexion on both sides. Muscle sense and appreciation of sharp and dull were impaired in both legs. Appreciation of hot and cold were somewhat diminished over both legs, as high as the knees. Appreciation for touch was diminished over the left leg and the left foot. The blood pressure was 126/76.

Laboratory.—Hb. = 46%. R. B. C. = 1,430,000. W. B. C. = 13,050. Vital staining R. B. C. = 0.2%. The urine showed a faint trace of albumin, some hyaline and granular casts, and many W. B. C. in clumps. The urine gave a positive test for urobilin.

For ten days after admission the patient was kept on an experimental fat-free diet without any improvement in the blood picture.

TRANSFUSIONS

XV. Five hundred and fifty cubic centimeters of matched and grouped whole blood. Citrate method. The blood was run in very slowly. After receiving about 175 cubic centimeters of blood, the patient's respirations became somewhat sighing in character and then slightly dyspnoeic. The transfusion was discontinued. The patient began to shake violently, but did not feel chilly. An hour later the temperature had risen to 104.6° F. She vomited and became somewhat irrational. She went to sleep at 8 P. M. and could not be roused during the night. On the following day the temperature remained elevated. The scleræ and skin were quite yellow. The patient was in a very low mental state; she seemed to be able to fix her attention, but did not respond to questions. She had not voided sixteen hours after the transfusion, and was catheterized for 350 cubic centimeters of reddish orange colored urine, containing many hyaline and granular casts and a few R. B. C. The urine gave a strongly positive test for hemoglobin with benzidine. Donor, Co. The blood of both the patient and the donor were regrouped; they were both Group IV. In rematching, on first trial there was a perfect match; on second trial, the recipient's serum *vs.* the donor's cells gave no agglutination or hemolysis; the donor's serum *vs.* recipient's cells gave no agglutination, but did give very slight hemolysis as shown by the presence of a few "shadows" under high power examination of the specimen. All incubations were carried on for at least one hour, usually longer.

III-21-20. The patient could be roused with difficulty and would respond to questions. There were marked herpes labialis and herpes zoster.

III-28-30. The patient had involuntary stools and involuntary voiding at times, but usually had to be catheterized. There was twitching of the upper extremities, and the stream of talk was occasionally incoherent and irrelevant. The pulse grew weak, but responded to strophanthin.

IV-2-20. The blood urea nitrogen was 74 mgm. per 100 cubic centimeters. The carbon dioxide of the plasma was 44.7 vol. %. The patient showed a constant temperature elevation as high as 102.8° F., and continued to require catheterization. Cystitis had become very marked and the urine showed a large amount of ropy pus in the specimen bottle. A urine culture showed a marked growth of *B. coli*. She began to have seizures, manifested by the loss of consciousness, and lasting from one to ten minutes. There was fixation of the eyes, twitching of the facial muscles, and coarse jerky movements of the hands and arms. Sometimes they began with hiccup, wretching, and vomiting of a light brown fluid. There was occasionally a very slow lateral nystagmus. During these attacks, the respiration became rapid and labored and there was foaming at the mouth. The radial pulse rate in these seizures was one half of the rate before or after the attack, and corresponded with the rate counted at the cardiac apex. For a period of a week the patient had numerous such seizures during the day and night, at the end of which time they ceased.

IV-4-20. Carbon dioxide of the alveolar air was 24 vol. %. A blood culture gave no growth.

XVI. As the patient had had such extremely severe reactions in previous transfusions, it was decided to attempt a transfusion of the serum of Group I, which contains no isohemolysins or isoagglutinins. A Group I donor was obtained and 500 cubic centimeters of blood was withdrawn in the usual method, and allowed to clot over night in the ice-box; the following day 235 cubic centimeters of the supernatant serum was pipetted off; centrifugalised at high speed to remove all cellular elements and inactivated at 56° C. for one hour. The serum was then diluted with 100 cubic centimeters of normal salt solution to render it less viscous. The diluted serum was injected intravenously in the usual method, by gravity. There was no reaction of any sort. Donor, O., Group I.

IV-18-20. The patient gradually became rational. The two small infected hypodermic areas which had followed the injection of strophanthin a week previously showed improvement. An early bedsore on the right buttock showed no improvement. There was

complete paralysis of both lower extremities, and complete loss of muscle sense, and of all sensations as high as the umbilicus.

IV-25-20. The patient's condition became very unsatisfactory. Her respirations became rapid and shallow with periods of hyperpnœa, and the pulse rapid, feeble and irregular. The temperature ranged from 101° (R) to 104.4° (R). The psyche was in a twilight state. There was a myocardial death at 8.10 P. M., with a temperature of 105° F. at death.

Analysis.—The patient in Case III had six admissions to the hospital in a little less than three years and during this period received about eight and one-half liters of blood in 15 transfusions, and 235 c. c. of blood serum in one transfusion. She suffered six reactions of varying degrees of severity, showing hemoglobinuria on two occasions. From the time at which she first came under observation until the development of a marked cystitis, and later, the transfusion of serum, the blood picture showed very little regenerative activity. Whether the evidences of bone-marrow stimulation, shown by the blood picture from April 2, 1920 until the time of death, resulted from the cystitis and hypodermic infections, or from the transfusion of Group I serum, it is impossible to say. However, the picture shows greater bone-marrow activity following the administration of blood serum. It is rather interesting that the hemoglobin and R. B. C. determinations showed a progressive improvement until the time of death. The acidosis shown by this case has been described by Barskey and Kahn[6] as one of the findings in pernicious anemia.

In endeavoring to explain these very severe reactions the first question which naturally presents itself, is: Were the donors' bloods really compatible with those of the recipients'? In all of the matchings carried out before transfusion the bloods apparently were compatible. In Case I, Transfusion V, the incubation of the preparations was carried on for only 30 minutes; hence we may reasonably assume that up to this time 30 minutes had been the usual incubation period in the routine blood matchings. Thereafter the preparations were allowed to incubate for one hour or longer. In Cases I and II the matchings were performed by the bacteriological laboratory; and in Case III all tests for compatibility were examined by at least two persons before being pronounced acceptable. In no instance were donors used when examination had shown either agglutination or hemolysis.

The blood groups of Cases I and II are not known. Case III was repeatedly found to belong to Group IV and only Group IV donors were used for transfusion of whole blood. This fact lends additional interest to the severity of the reactions experienced by Case III, as it has been stated by Drinker and Brittingham,[7] and reaffirmed by Lee[8] that the members of

CASE III

Date	Hb.	R. B. C.	W. B. C.	P. M. N.	P. M. E.	P. M. B.	S. M.	L. M.	Tr.	Myelocytes	Anisocytosis	Poikilocytosis	Punctate basophilia	Diffuse basophilia	Nucleated R. B. C.	Macrocytes	Microcytes	Platelets	Vital staining R. B. C.	Transfusions
VII-21-17	10	980,000	3,640	..	..	..	..	..	..	..	+++	+++	+	+	0	....	....	Few.	..	7-23-17 425 c. c.
VII-27-17	27	1,448,000	4,200	..	..	..	..	..	..	..	....	....	..	..	..	....	....	.....	..	7-30-17 500 c. c.
VIII- 8-17	38	1,688,000	5,000	..	..	..	..	..	..	..	....	....	..	..	..	....	....	.....	..	8- 9-17 500 c. c.
VIII-19-17	41	1,808,000	2,400	..	..	..	..	..	..	..	....	....	..	..	..	....	....	.....	..	8-21-17 500 c. c.
XI-26-17	68	2,248,000	7,480	56.0	6.0	.0	35.0	5.0	2.0	.0	++	++	..	..	0	....	....	Few.	..	12- 4-17 400 c. c.
XII-16-17	70	2,860,000	6,200	49.0	6.0	1.0	38.0	6.0	.0	.0	++	++	..	..	0	....	....	Few.	..	12-18-17 400 c. c.
XII-20-17	70	3,460,000	....	..	..	..	..	..	..	..	....	....	..	..	..	....	....	.....	..	Second admission.
I-10-18	74	3,520,000	6,200	64.0	5.0	.0	26.0	5.0	.0	.0	++	+	0	0	0	+	....	Few.	..	1-21-18 1150 c. c.
II- 2-18	57	2,680,000	5,800	63.0	4.0	.0	25.0	7.0	1.0	.0	....	....	..	..	..	....	....	.....	..	2- 5-18 1000 c.c.
II-16-18	71	3,500,000	6,100	..	..	..	..	..	..	..	....	....	..	..	..	....	....	.....	..	Third admission.
V-18-18	70	2,736,000	4,600	..	..	..	..	..	..	..	+	+	..	..	..	....	....	... .	..	5-27-18 700 c. c.
V-29-18	82	2,720,000	4,800	..	..	..	..	..	..	..	+	+	..	..	+	....	....	.....	..	6- 6-18 500 c. c.
VI-18-18	85	2,700,000	5,160	..	..	..	..	..	..	..	....	....	..	..	..	. ..	....	.....	..	Fourth admission.
XI-14-18	75	3,056,000	11,800	53.2	2.8	.0	41.2	2.8	.0	.0	+	+	0	0	0	+	++	Normal.	..	11-16-18 450 c. c.
XI-19-18	80	3,528,000	6,800	62.0	4.0	.4	32.0	.8	.8	.0	+	+	0	0	0	....	....	Decr'd.	..	11-21-18 500 c. c.
XI-26-18	100	4,008,000	7,700	53.2	2.4	.8	?	3.6	.0	.0	0	0	0	0	0	....	....	Normal.	0.8	Fifth admission.
VI- 5-19	45	1,856,000	5,100	55.2	8.0	.0	36.4	.4	.0	.0	+++	+	0	+	1.0	++	....	Decr'd.	0.1	6- 7-19 500 c. c.
VI-15-19	43	1,472,000	4,700	37.6	6.0	.4	52.0	2.4	.0	1.6	++	++	0	0	0	....	....	Very few.	..	6-16-19 450 c. c.
VIII-28-19	85	2,400,000	10,000	..	..	..	..	..	..	..	....	....	..	..	..	....	....	.....	..	Sixth admission.
III- 5-20	43	1,470,000	4,800	59.0	4.0	.0	36.0	1.0	.0	.0	+++	+++	0	+	0	+++	....	Very few.	0.2	3-19-20 175 c. c.
III-20-20	27	990,000	5,500	78.0	.0	.0	22.0	.0	.0	.0	++++	+++	0	+	0	....	....	None seen.	..	Cystitis developed.
IV- 2-20	26	770,000	17,650	90.0	.0	.0	10.0	.0	.0	.0	++++	+++	0	0	0	....	....	Decr'd.	..	.....
IV- 7-20	20	790,000	15,500	83.0	1.0	.0	15.0	.0	1.0	.0	++++	+++	0	+	3	....	....	Decr'd.	..	4- 7-20 235 c. c. of Gr. I serum.
IV- 9-20	20	710,000	15,350	80.0	4.0	.0	11.0	3.0	2.0	.0	++++	+++	0	+++	19	....	....	Few.	..	.....
IV-24-20	46	1,430,000	13,050	83.0	.0	.0	13.5	2.0	.5	1.0	++	++	0	0	0	....	....	Few.	..	.....

Group IV are universal donors, and may give blood for use with recipients of any other group. Lee states that donor and recipient need not be in the same blood group if the serum of the recipient does not agglutinate or hemolyze the R. B. C. of the donor, because the blood of the donor will make up only one-fifth to one-twelfth of the total blood volume of the recipient, and the donor's serum is thus diluted; moreover, the recipient's cells are protected by his own serum. Drinker and Brittingham have suggested that *in vitro* reactions are occasionally unreliable and Sydenstricker and others[3] state that it is safer to give recipients of other groups the washed R. B. C. of Group IV, than to attempt to use the whole blood. Case III proves conclusively that there are instances in which Group IV blood cannot be used with impunity, even in a member of the same group.

In an attempt to explain the mechanism of the reactions it is obvious that the reactions must have been due to either: (1) imperfect technic; (2) unavoidable factors in the procedure of transfusion; (3) or some undemonstrable incompatibility of the blood used.

There seems to be no reason for questioning the technic, as a uniform technic has been employed throughout the series, and a very large number of other cases have been transfused in the same manner without suffering serious reactions. Of necessity the Lindemann transfusions were always performed in the same manner. With the citrate method the apparatus offers one factor for discussion, since it has been shown by Stokes and Busman[5] that a certain type of new rubber tubing is responsible for some of the reactions to arsphenamin; they suggest that this may be a contributory factor to reactions with other intravenous methods. However, it is known that during the sixth admission of Case III the same apparatus, without change, had been used repeatedly on other cases without any reaction.

In an exhaustive study on the causes of reactions to citrate transfusions, Drinker and Brittingham[7] discuss factors which seem to be unavoidable in the present state of knowledge about transfusion. They conclude that reactions are due to: (1) Changes in the blood platelets, a part of the process of coagulation, (2) direct action of sodium citrate on R. B. C., rendering them more fragile and promoting hemolysis; (3) very rare gross incompatibilities which escape *in vitro* detection.

Coagulation has been considered a factor of importance by Novy and De Kruif,[9] who have shown experimentally with animals that blood becomes highly toxic in the precoagulation stage, and that the effects produced are those of anaphylatoxin, producing the same picture as anaphylactic shock. However this factor enters into every transfusion and as a rule we do not see severe reactions as a result of it.

In citrate transfusion the action of sodium citrate in rendering the red blood cells more fragile and thus promoting hemolysis may be a contributory factor. On the other hand the degree of hemolysis cannot be great, as Drinker and Brittingham do not mention having observed hemoglobinuria in any of their cases, while in the series under consideration, hemoglobinuria occurred four times, excluding transfusion V in Case I, in which the blood was later shown to have been incompatible. Moreover, it is far from proven that hemoglobin is as toxic as it is generally considered to be. Sellards and Minot,[11] in a study of the relationship between experimental hemoglobinuria and blood destruction in man, produced hemoglobinuria by the intravenous injection of the hemoglobin obtained from 4 c. c. to 33 c. c. of laked human R. B. C. They state: "One of the striking features of these injections is the absence of subjective symptoms after these comparatively large injections of hemoglobin. One normal patient received 28 c. c. of laked cells without any subjective symptoms and showed a slight hemoglobinuria. Another normal individual received 33 c. c. of laked cells. An hour after the injection a short mild chill developed which lasted about ten minutes, but it was not accompanied by nausea or headache. The patient became entirely comfortable after this chill, but during the first half of the night he did not sleep on account of flushing and a succession of hot and cold sensations. There was an intense hemoglobinuria and this discomfort continued for several hours after the active excretion of hemoglobin in the urine had ceased. The donor of cells for hemoglobin in this case was a member of Group IV." Twelve other cases showed varying degrees of hemoglobinuria without any subjective symptoms. They suggest that there are other factors in addition to the setting free of hemoglobin which play a rôle in the production of symptoms in those cases having some hemolysis following a transfusion. Likewise, Bayliss[12] has concluded from experimental injections of hemoglobin in cats that hemoglobin is non-toxic; he also found the stroma of the red blood cells to be non-toxic. In summarizing his results, he states, "It appears that the serious results of the transfusion of incompatible blood are not to be ascribed to the hemolysis as such, but are rather an aspect of the action of foreign serum protein analogous to that responsible for anaphylactic shock." Furthermore, Minot and Lee report three instances of reactions identical with those under consideration, but they do not state how many previous transfusions the patients had received. In one case they believe that the procedure hastened the patient's death, while in two cases it did not do so. They state, "In the case in which death was hastened the patient received in 12 days three transfusions of about 400 c. c. each. Following the first two there was no reaction, while following the third, from the same donor as was used for the first, the patient complained at once, particularly of headache; shortly vomiting occurred, the patient became toxic, the temperature rose, and marked jaundice developed, and he died in about 18 hours. No hemoglobinuria occurred. Another sick patient, shortly following a transfusion from a donor whom she had previously received blood from without ill effects, developed a similar severe reaction. The reaction consisted of a chill, temperature 102.5° F.; gastric symptoms and rapidly marked jaundice developed. Very slight hemoglobinuria occurred. Death occurred two weeks later. A similar, much less severe reaction occurred in a third very sick patient who died five days after the fourth transfusion in three weeks. The isoagglutination tests in these three cases showed no agglutination

or hemolysis and we verified them after the reactions in the first two cases. The donors and patients belonged to the same isoagglutination groups. Though these reactions may be of some sort of an isohemolytic nature, they are not of the known type. It would seem that they may have been due to the development by previous transfusions of some unknown and unrecognized antibody to the donor's blood." They further suggest that the reaction may have been due to a lowered tolerance to blood pigments which had accumulated during the blood destruction incident to the disease, and from the destroyed blood of previous transfusions, and that the subsequent introduction of more pigment had been sufficient to produce signs of toxicity.

The latter explanation does not seem so attractive as the former, since their argument is substantiated by the fact that the case which died had received the hemoglobin from 17 c. c. of laked R. B. C. in a previous experimental intravenous injection and had reacted with "marked toxic symptoms and an intense hemoglobinuria," whereas following the transfusion the reaction was more severe and there was no hemoglobinuria.

The statements of Novy and De Kruif, Sellards and Minot, Bayliss, and Minot and Lee thus have some bearing on the question of undemonstrable incompatibilities of blood producing severe reactions in transfusion. The manifestations of the reactions in the three cases under consideration are particularly suggestive of an anaphylactic reaction, as the picture resembles the immediate reaction occurring in "serum sickness" with dyspnœa, cyanosis and particularly urticaria. All three cases showed urticarial eruptions during the series of transfusions, and Case I, after one transfusion complained of puffiness about the eyes, although no œdema of the skin was noted. On another occasion the pains in the arms may have been joint pains. The tenability of the belief that the reaction is anaphylactic is further strengthened by the inability to demonstrate any incompatibility of the blood used, for the blood undoubtedly was incompatible in every instance in which a severe reaction occurred. This assumption would account for the absence of agglutination or hemolysis in the blood matchings, and we might expect to find a precipitin reaction between the incompatible bloods. It was considered desirable to study Case III from this viewpoint, but the opportunity did not present itself, as it would be necessary to have the donor's and recipient's blood before and after a transfusion in which a severe reaction had occurred.

A study of the foregoing cases emphasizes the importance of a few practical considerations, some of which have been stated before. The most significant fact is that there are certain cases of pernicious anemia in which it becomes increasingly difficult with successive transfusions to find compatible donors, and in which severe reactions will occur, no matter how carefully blood matching is carried out. In the present state of our knowledge of means for determining the compatibility of blood, transfusion is a self-limited process, and until more suitable methods are devised for blood matching no attempt should be made to transfuse these cases. The inadvisability of further attempts at transfusion should be indicated by the discovery that the patient reacts badly, particularly with hemoglobinuria, although no discrepancy is demonstrable upon rematching donor and recipient. As a matter of conjecture, it may be found by precipitation methods with the use of a hemolytic series that suitable donors are available for these cases, as precipitation tests are much more delicate than agglutination tests and might reveal a lesser degree of incompatibility. Furthermore, blood matchings should be carried out with the most extreme care and no preparation should be passed upon favorably in which the field does not show a perfectly uniform distribution. The period of incubation, except in emergencies, should be at least two hours, for Walter Baetjer[14] has seen some instances in which the bloods were slow agglutinators and produced no definite change in the preparation in one hour. The preparations should be examined for uniform distribution immediately after being set up. Whenever possible, the preparation should be allowed to incubate over night and be read on the following day. Whenever a recipient begins to show signs of reaction the transfusion should be discontinued at once; any remaining blood could be injected at the end of one or two hours if a severe reaction had not occurred. Pemberton[15] reports three deaths in which transfusion was completed after the beginning of a reaction. The development of an urticarial wheal during the course of a transfusion should be the sign for immediate cessation of the operation, and it seems doubtful whether the remainder of the blood should be used later.

Conclusions

1. In certain patients suffering from pernicious anemia, who have been transfused repeatedly, transfusion becomes self-limited because of the inadequacy of methods for selecting suitable donors.

2. This difficulty having once been discovered, no attempt should be made to transfuse these patients.

3. The severe reaction is probably due to an anaphylactic manifestation, and not to hemolysis *per se*.

4. Blood matching should be carried out with the greatest care; whenever possible, the incubation period should be at least two hours, or longer.

5. Blood serum free from cellular elements may produce bone-marrow stimulation.

6. Members of Group IV cannot be regarded absolutely as universal donors.

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THE FATE OF TRUE SOLUTIONS (PHENOLSULPHONEPHTHALEIN) AND COLLOIDS (TRYPAN BLUE) INJECTED INTO THE MAMMALIAN EMBRYO

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Savory, in 1857, was the first investigator to inject a substance into a living fetus and observe its appearance in the mother. He injected acetate of strychnine into two out of four fetuses in a dog. Nine minutes after the injection the mother exhibited tetany and died 28 minutes later. The two injected fetuses were dead; the uninjected fetuses were alive and showed no symptoms of tetany. He also injected two fetuses in a cat; 10 minutes later the mother showed signs of tetany and died in 17 minutes. The injected fetuses, although showing tetany, survived the mother; two uninjected fetuses showed no tetanic symptoms. He then injected six fetuses in a rabbit. The mother died in 18 minutes; the fetuses, which all showed signs of tetany, survived the mother for a short period. In another experiment, after strychnine had been injected into four fetuses in a dog, the animal showed tetanic spasms after 30 minutes. Savory noted that in nearly all his experiments the fetuses were less susceptible to strychnine than the mother.

Savory's interesting observations were confirmed by Gusserow (in 1878) who injected a series of 24 pregnant rabbits, 7 dogs, and 5 cats with strychnine. His results were very similar to Savory's. He noted that the more advanced the gestation, the more rapidly strychnine passed from fetus to mother. Strychnine convulsions appeared in the mother in from 11 to 36 minutes after the injections, and usually resulted in death in from 30 to 45 minutes. Gusserow concluded, from Savory's experiments and from his own, that substances can pass from fetus to mother.

Preyer (in 1885) observed the passage of several other substances from fetus to mother. He injected 0.2 c. c. of a 12 per cent solution of hydrocyanic acid into a mature fetal guinea-pig; two minutes later the mother had convulsions, became dyspnoeic and died after four minutes. The injected fetus was dead; and uninjected one was still alive at the time of death of the mother. In another similar experiment the mother exhibited convulsions one and one-half minutes after the injection of 0.2 c. c. of a 12 per cent solution of hydrocyanic acid. Preyer also experimented with nicotine. This drug, when injected into several guinea-pig fetuses, produced clonic convulsions in the fetuses in one and a quarter minutes, but in the mother only mild symptoms of poisoning, which did not result in death.

In another experiment a quantity of curarine, sufficient to kill an adult guinea-pig in 15 minutes, was injected into a guinea-pig fetus. The mother became completely paralysed and died in 80 minutes. The injected fetus, as well as two uninjected ones, showed no symptoms of poisoning. Several other experiments with curarine gave similar results.

Lannois and Briau (in 1898) investigated the passage of several other substances from fetus to mother. They injected sodium salicylate into guinea-pig and rabbit fetuses, and in three instances found the drug excreted in the urine of the mother at the end of one hour. With potassium iodide three trials were negative, but in one instance they were able to detect the substance in the maternal blood stream at the end of an hour. With methylene blue they succeeded in recovering the substance from the maternal urine in five out of six attempts. At the end of two hours only chromogen was obtained from the urine, but in from six to seven hours the unchanged dye-stuff was finally excreted. They too observed that the passage of substances from fetus to mother was most rapid near term.

Baron and Castaigne (in 1898) found that potassium iodide, injected into guinea-pig fetuses, appeared in the maternal urine in 40 minutes. When injected early in pregnancy they noted the passage of the same drug in 30 minutes. Methylene

blue injected underneath the scalp of a human fetus during labor appeared in the maternal urine in one-half hour. They found that the substances do not appear in the urine if the fetuses are dead.

Guinard and Hochwelker (1899) observed the passage of rosanilin from fetus to mother in four instances, the shortest interval required for the drug to reach the maternal urine being 25 minutes. They found that death of the fetus invariably suspends the fetal-maternal passage of a substance. They injected strichnine and aconite repeatedly into dead fetuses without any effect upon the mother.

Charrin (1898) injected diphtheria toxin into fetuses and observed symptoms of intoxication from it in the mother.

Kreidl and Mandl (1903) injected atropine, adrenalin, pilocarpine, physostigmine, and phloridzin into a number of rabbit, cat, dog, goat and monkey fetuses. Atropine (1 c. c. of a 1 per cent solution) caused dilatation of the pupils in the mother, commencing 10 minutes after the drug had been injected into the fetuses. Pilocarpine (several cubic centimeters of a 1 per cent solution) caused extreme salivation in the mother within 10 minutes after its injection. The passage of physostigmine was demonstrated by injecting it into the fetuses of an animal which had been previously curarinized. On the injection of physostigmine the sciatic nerve resumed its irritability toward electric stimuli. Finally, phloridzin was shown to cause melituria in the mother within three hours following the injection of several cubic centimeters of a 5 per cent solution into the fetuses. Adrenalin was the only drug from which an effect on the mother could not be demonstrated. Numerous experiments with adrenalin led to the conclusion that it decomposes and loses its pharmacological activity before it traverses the placenta. Kreidl and Mandl mentioned no differences of time required by the drugs to pass from fetus to mother in the various species of animals employed by them.

In addition to the observations upon the fetal-maternal passage of substances which have been injected directly into the fetuses, several experimenters have investigated the possibility of substances passing from the amniotic fluid into the maternal blood stream. Thus Gusserow (1858) injected strychnine into the amniotic sacs of a series of rabbit, cat, and dog fetuses. In three of these experiments the mother showed symptoms of strychnine poisoning in 15 to 20 minutes. In seven others strychnine poisoning failed to develop in the mother. Preyer (1885), analyzing Gusserow's work, came to the conclusion that the three positive experiments afforded excellent proof of the passage of substances from the amniotic fluid into the maternal blood stream. In the seven negative experiments he was able to point to some technical error, the use of chloroform, or the death of the fetus, as an explanation for the failure of the strychnine to produce poisoning in the mother.

Bar (1881) undertook two similar experiments. He injected 20 drops of a strychnine solution into the amniotic sac of a rabbit fetus. After 20 minutes the mother had convulsions. He introduced a similar amount into the amniotic sac of a fetus of another animal: in 20 minutes the mother had severe convulsions.

Toerngren (1888) injected iodide of potassium in doses of one or two grams into the amniotic sacs of rabbits. The substance later appeared in the urine of the mother. The time required was at least 45 minutes, and passage occurred whether the fetuses were at term or in the middle of development.

In addition to the question of transmission of substances injected into the fetus through the placenta, the possibility of excretion by the Wolffian body and the metanephros during fetal life have been investigated experimentally. Thus, Wiener (1881) injected sodium indigo sulphonate through the uterine wall into the subcutaneous tissue of several dog fetuses. In 25 minutes the substance appeared in the convoluted tubules of the kidneys, and a few minutes later in the fetal bladders. The substance similarly injected into rabbit fetuses appeared in 20 minutes in the convoluted tubules, and subsequently in the fetal bladders. The glomeruli remained uncolored. Wiener also injected diluted glycerine subcutaneously into rabbit fetuses, whereupon hemoglobinuria resulted in one and a half hours. He also injected a solution of potassium ferrocyanide into the amniotic sac of a rabbit and after two and a half hours detected it in the fetal urine.

Bar (1881) repeated Wiener's experiments, using potassium ferrocyanide. At the end of 40 minutes several drops of urine in the bladder gave the Prussian blue reaction.

Bakounine (1895) injected indigo carmine into the omphalomesenteric vessels or the aorta of developing chicks, and observed the excretion of the coloring matter by the tubules of the Wolffian body. The glomeruli never exhibited the dye.

Recently Firket (1920) has reported the results of injecting a solution of sodium ferrocyanide and iron ammonium citrate into the umbilical vein of cat fetuses. On sacrificing the mothers at intervals varying from 15 minutes to several hours and examining the fetuses, Prussian blue was observed in the convoluted tubules, urine, and allantoic fluid.

Mention must also be made of the experiments of Krukenberg (1885) on rabbits. After the injection of potassium iodide into the maternal blood stream he found traces of the substance in the fetal kidneys.

In the present experiments the fate of phenolsulphonephthalein and trypan blue injected into fetuses was investigated. Phenolsulphonephthalein was selected because it is a crystalloid, diffuses readily and is non-toxic. Trypan blue was used because its forms a colloidal solution, is relatively non-toxic and its behavior in the adult organism is well understood.

Phenolsulphonephthalein

Phenolsulphonephthalein was injected into a series of cat and guinea-pig fetuses by the following technique: The pregnant animal was anæsthetized with ether, a laparotomy performed, the bladder exposed, the urethra ligated, and a bent glass cannula tied into the bladder. The cannula was allowed to drain into a beaker containing a 1 per cent solution of sodium hydroxide. The uterus was next exposed and a fetus palpated. A syringe containing sterile phenolsulphonephthalein solution and bearing a 16-gauge needle was inserted

through a nick in the uterine wall, through the fetal membranes into the peritoneal cavity of the fetus. One cubic centimeter of phenolsulphonephthalein was injected into the peritoneal cavity of the fetus and the syringe withdrawn. The uterus was carefully replaced in its normal position and the laparotomy opening closed. The animal was kept under light anæsthesia. The interval elapsing between the time of injection and the first appearance of the dye in the maternal urine was noted; as soon as this occurred the animal was sacrificed. The fetuses were removed from the uterus, and the bladder content of the injected fetus was tested for phenolsulphonephthalein. The urine of the adjacent fetuses and fluid contained in their membranes were also tested for the presence of the dye. The results of these experiments are presented in Table I.

It will be seen that phenolsulphonephthalein, when injected into the peritoneal cavity of the fetus, is absorbed by the fetal blood-stream and conveyed to the placenta, through which it slowly diffuses into the maternal circulation. The time required for the drug to appear in the mother is quite variable for individuals of the same species. No difference is observed between the cat and guinea-pig in the time required for the passage of the dye from fetus to mother. Further, it is seen that phenolsulphonephthalein is readily excreted by the fetal kidneys, for it was found in the fetal bladder in every instance in which sufficient urine could be collected to test for its presence. None of the drug could be detected in the urine or amniotic fluid of the adjacent uninjected fetuses.

TRYPAN BLUE

Trypan blue (1 c. c. of a 0.5 per cent solution) was injected into the peritoneal cavities of cat and guinea-pig fetuses by a similar technique. Table II shows the results of these experiments.

It will be observed that trypan blue could not be detected in the maternal urine during the period of 5 hours while the animals were under observation. At the termination of the experiment the dye in every instance was found in the fetal kidneys. No trypan blue was observed in the uninjected fetuses.

In a second set of experiments trypan blue was injected into the peritoneal cavities of the fetuses under aseptic precautions. After closing the abdomen of the pregnant animal it was allowed to recover from anæsthesia. The animals were finally sacrificed at intervals of 24, 48 and 72 hours, respectively. In none of these cases was trypan blue found at any time in the maternal urine.

In every instance in which the mother was allowed to survive 24 hours or longer, the fetus which had received an injection of trypan blue was found vitally stained. In the gross the staining was quite striking. The placenta and fetal mem-

TABLE I

Animal	Crown-rump length of injected fetus	Substance and quantity injected	Where injected	Time of appearance in maternal urine	Urine of injected fetus	Urine and amniotic fluid of uninjected fetuses	Condition of injected fetus at time of removal from uterus
Guinea-pig 1...	95 mm.	1 c. c. phenolsulphonephthalein.	Intraperitoneally.	1 hr. 45 minutes.	Positive.	Negative.	Living.
Guinea-pig 2...	112 mm.	1 c. c. phenolsulphonephthalein.	Intraperitoneally.	55 minutes.	Undetermined.	Negative.	Living.
Guinea-pig 3...	67 mm.	1 c. c. phenolsulphonephthalein.	Intraperitoneally.	1 hr.	Positive.	Negative.	Living.
Guinea-pig 4...	118 mm.	1 c. c. phenolsulphonephthalein.	Intraperitoneally.	40 minutes.	Positive.	Negative.	Living.
Guinea-pig 5...	106 mm.	1 c. c. phenolsulphonephthalein.	Intraperitoneally.	55 minutes.	Positive.	Negative.	Living.
Cat 1.....	105 mm.	1 c. c. phenolsulphonephthalein.	Intraperitoneally.	1 hr.	Positive.	Negative.	Living.
Cat 2.....	116 mm.	1 c. c. phenolsulphonephthalein.	Intraperitoneally.	2 hrs. 25 minutes.	Positive.	Negative.	Living.
Cat 3.....	125 mm.	1 c. c. phenolsulphonephthalein.	Intraperitoneally.	2 hrs. 15 minutes.	Undetermined.	Negative.	Living.
Cat 4.....	115 mm.	1 c. c. phenolsulphonephthalein.	Intraperitoneally.	45 minutes.	Positive.	Negative.	Living.
Cat 5.....	87 mm.	1 c. c. phenolsulphonephthalein.	Intraperitoneally.	1 hr. 35 minutes.	Positive.	Negative.	Living.

TABLE II

Animal	Crown-rump length of injected fetus	Substance and quantity injected	Where injected	Time of appearance in maternal urine	Urine of injected fetus	Urine and amniotic fluid of uninjected fetuses	Condition of injected fetus at time of removal from uterus
Guinea-pig 1...	92 mm.	1 c. c. 0.5% trypan blue.	Intraperitoneally.	None in 5 hours.	Positive.	Negative.	Living.
Guinea-pig 2...	122 mm.	1 c. c. 0.5% trypan blue.	Intraperitoneally.	None in 5 hours.	Positive.	Negative.	Living.
Cat 1.....	75 mm.	1 c. c. 0.5% trypan blue.	Intraperitoneally.	None in 5 hours.	Positive.	Negative.	Living.
Cat 2.....	32 mm.	1 c. c. 0.5% trypan blue.	Intraperitoneally.	None in 5 hours.	Positive.	Negative.	Living.

branes of the injected fetus were dark blue, while the uterine musculature and decidua in the region of the injected fetus were unstained. No staining of the placentæ or membranes of the neighboring uninjected fetuses was observed. On rupturing the membranes of the injected fetus the amniotic fluid was observed to be quite blue. In the cat fetuses an additional blue coloration was noted in the allantoic fluid. The umbilical cord, as well as the fetus itself, appeared deep blue. On gross sagittal section of the fetus its tissues were observed to be uniformly blue with the exception of the brain and cord, which were unstained.

A detailed description of the microscopic appearances of these vitally stained fetuses will be reserved for a future paper, but the main features of the staining will be here briefly outlined. Trypan blue occurs in many of the tissues of the fetus in the form of characteristic cytoplasmic granules. It occurs most abundantly in the liver and kidneys. The Kupffer cells of the liver contain numerous tiny, brilliant blue granules within their cytoplasm. The epithelial cells of the convoluted tubules of the kidneys are heavily laden with blue pigment. Trypan blue has not been deposited elsewhere than in the convoluted tubules, for the glomeruli and collecting tubules are unstained. So-called clasmatocytes, pigmented with trypan blue, occur throughout the loose connective tissue of the fetus. The cells constituting the delicate stroma of the umbilical cord and fetal membranes contain minute granules of dye within their cytoplasm. The amniotic epithelium contains similar cytoplasmic granules. In the placenta the dye occurs in the form of tiny granules in the cytoplasm of the cells which form the delicate stroma supporting the fetal vessels. It is also observed in the endothelial cells of the placental capillaries. Dye is not seen in the chorionic epithelium or in any of the maternal elements of the placenta.

The liver and kidneys of the mother were examined microscopically for trypan blue, but no trace of the dye could be discovered.

Summary

1. Phenolsulphonephthalein, which represents an easily diffusible, non-toxic dye, is absorbed from the peritoneal cavity of the fetus. It passes slowly from the fetal blood stream through the placenta into the maternal blood stream and is excreted by the maternal kidneys. It is also excreted by the fetal kidneys, since it is found in the fetal urine. This observation demonstrates that the fetal kidneys are capable of excretion, but sheds no light on the extent to which they act as a pathway of excretion before birth. No difference was noted between the cat and the guinea-pig as to the time of transmission of the dye by the placenta, but a marked difference in the time required was observed in individuals of the same species.

2. Trypan blue, a less diffusible, non-toxic colloidal dye, is also absorbed from the peritoneal cavity of the fetus. It is not excreted in the maternal urine, and microscopic examination shows that it is not transmitted by the placenta to the maternal organism. It is excreted by the fetal kidneys. The observations with trypan blue show that the placenta is incapable of transmitting an inert foreign colloid from fetus to mother, and hence it is probable that the placenta does not transmit the colloidal products of fetal excretion unless they are first converted into simpler, readily diffusible, substances.

3. The fetus becomes vitally stained after injections of trypan blue into the fetal peritoneal cavity. The dye is stored in the endothelial cells of the liver, and also accumulates in the ephithelial cells of the renal convoluted tubules. The dye is absorbed by clasmatocytes which occur throughout the fetus and in the placenta and fetal membranes.

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PROCEEDINGS OF SOCIETIES

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY

DECEMBER 6, 1920

1. Drainage of the Common Bile-Duct through the Cystic Duct. Cystico-choledochostomy. (Abstract.) DR. MONT R. REID.

Twelve months ago Dr. Halsted and I made a brief report to this Society on the subject of drainage of the common bile-duct. Up to that time the ductus choledochus had in four instances been drained in the manner about to be described, two of the patients being exhibited at the meeting. In a letter to the editors of the *Journal of the American Medical Association* (published December 20, 1919, vol. 73, pp. 1896 and 1897) Dr. Halsted advocated the careful and complete closure of the incision into the ductus choledochus and the drainage of this duct by a tube passed well into it by way of the ductus cysticus. For this procedure he proposes the term cystico-choledochostomy, aware, of course, that the choledochotomy is not embraced in it.

In our older hospital records we find that in a few instances a tube has been passed from the cystic into the common duct, but only in cases in which the common duct had not been incised. For example, in 1899, Dr. Halsted being able to remove stones from the common bile-duct by forcing them back through the cystic duct, drained the former by a tube passed through the latter. Similarly, Sowers in 1904 drained the common duct through the short stump of a friable cystic duct. Finney and Follis, also for the same obvious reason, drained the common duct in this manner in 1903 and 1904. In none of these cases, however, had the common duct been incised.

On March 24, 1917, Dr. Halsted first employed the method which we now advocate for all cases in which there is no definite contraindication. The patient, a woman 56 years old, was intensely jaundiced. A shrunken, chronically inflamed gall-bladder containing stones was excised, and several large soft stones were removed through an incision into the greatly dilated common duct. A catheter, No. 19, French, was passed through the cystic into the common duct and retained by a suture of catgut, No. 00. The long incision in the common duct was carefully closed with two rows of interrupted chromic catgut (No. 0) sutures. About this tube four small drains were placed. The patient's convalescence was remarkably rapid. All of the drained bile came by way of the tube and thus could be accurately measured. On the fourth day the tube was clamped for 11 hours; on the fifth for a longer period. As the clamping caused the patient no distress and as there was no peritubal leakage, the tube was removed on the sixth day. Except for a faint stain on the first dressing there was no evidence thereafter of even a drop of bile in the sinus tract. The wound healed promptly and the patient walked out from the hospital three weeks after admission. Thus, for the first time in this clinic, drainage of a sutured choledochus was maintained by a tube passed into it through the ductus cysticus. In the previous cases of cystico-choledochostomy the common duct, as stated above, was not incised, the stones having been removed through the cystic duct.

Although the impression made by this experience was a profound one, it was not until Dr. Halsted, two and one-half years later, had been operated upon for stones in the common duct and experienced the distressing consequences of the loss of all the bile for a period of three weeks, that he insisted upon the closure of the incision into the choledochus and the drainage of this duct by way of the cysticus, whenever possible. He had indeed requested that this procedure be adopted in his case, but as the cystic duct entered the common duct from behind, it was thought better, being simpler, to drain the choledochus in the orthodox fashion—in the way recommended and practised by surgeons the world over. On the second day bile began to leak about the tube and after the fourth day the tube (removed the fifth day) conveyed none of the bile which for three weeks poured in great quantities from the sinus. Food was positively repulsive, and the sense of taste was so far lost that frequently he seemed unable to distinguish one kind of food, meat or vegetable, from another, except by sight. By the 14th day emaciation and weakness were so marked that grave concern for his life was felt. In three weeks he lost 30 pounds in weight.

The operation is performed as follows: The cystic and common ducts being well exposed, the cystic artery ligated, the cystic duct clamped and divided about 2 cm. from its origin, the gall-bladder excised, the common duct incised and all discoverable stones removed, a probe, as large as possible, is passed into the duodenum. The stump of the cystic duct is then investigated and, if necessary, stretched with a clamp or other instrument. It is my preference to introduce the tube of the selected size through the cystic into the common duct before suturing the incision into the latter. The tube being properly located is maintained in place by one stitch of catgut No. 00, passed through its side and into the wall of the cystic duct. The incision into the choledochus is closed by one or, preferably, two rows of interrupted fine silk (No. 0) sutures. On several occasions I have used the finest catgut (interrupted sutures) for the inner row. One should test the line of suture by injecting salt solution through the tube. The suture line may then be protected from the drains by overlaid fat or other tissue. Three or four very thin Halsted drains or slender cigarette drains are placed about the rubber catheter. The cystic duct should be made to hug the catheter closely. It may ultimately seem advisable to employ a tube larger than those that we have been accustomed to use, but we must bear in mind the fact that the chief function of the tube is to relieve tension on the line of sutures of the common duct until union of this wound is firm. The employment of the largest possible size of tube in the hope that perhaps a stone may escape through it is inadvisable. Although small concretions have occasionally been known to pass by way of a tube, it is more than probable that, when this has occurred, others were left to find

their way into the duodenum by the natural route. The drains are removed, some on the second or third day, the remainder on the third, fourth, or fifth day. The catheter in the duct should not be disturbed until there is reason to believe that the wound in the common duct is firmly healed. In one instance it was left, as an experiment, for three weeks. Observations of various kinds were made during this period. On removal of the tube the bile, except for a few cubic centimeters, passed by the natural route.

When the cystic duct is obliterated, one should make, if feasible, a second opening into the choledochus, just large enough to admit a small tube, and completely close the original incision. I tested this in one case at Dr. Halsted's suggestion, and with satisfactory result. The outflow of bile ceased promptly on withdrawal of the tube. In all of our cases the tube has been directed towards Vater's diverticulum and in none of these did it become kinked or obstructed.

SUMMARY

1. Prolonged leakage of bile is distressing in its consequences to those who withstand it and has occasionally, both directly and indirectly, been responsible for the death of the patient.

2. The incision into the common duct should be closed and the tension on the suture line be relieved by a tube passed through the cystic duct.

3. This tube, if properly fitted, may function for weeks, conveying the bile, without peritubal leakage, to the surface.

4. On removal of the tube the discharge of bile through the fistula ceases either immediately or within a day or two, provided the common duct is not obstructed.

5. The patency of the duct may and should be tested by clamping the tube.

6. Healing of the abdominal wound is less likely to be delayed if uncomplicated by the leakage of bile—bile which is quite invariably infected.

7. Following removal of the cystico-choledochostomy tube there has been no leakage of bile in about half the cases, and no patient has drained externally a significant amount of bile for more than two days.

2. An End-to-End Anastomosis of the Large Intestine by Abutting Closed Ends and Puncturing the Double Diaphragm with an Instrument Introduced per Rectum. Dr. W. S. Halsted.

My interest in end-to-end suture (circular enterorrhaphy) of the intestine has had its exuviation periods. The impulse for the current experimental study was given by experiences in the case of a friend upon whom in the course of a very difficult and quite desperately serious operation for uterine and ovarian neoplasms it became necessary to excise a portion of the sigmoid flexure of the colon and to perform within the pelvis an end-to-end suture of this bowel. The operation, according to the testimony of competent observers, was performed in a masterly manner, the competent surgeon having the secure foundation that experimental work in the laboratory alone can give. A fecal fistula through which escaped all of the intestinal contents formed at the line of the circular suture, which presumably broke down more or less completely. For five weeks or more the patient had rigors and high fever, and when her life was almost despaired of the entire picture changed spontaneously within an hour or two and a rapid and uninterrupted convalescence followed. The operator was impressed with the filthiness of the methods of performing end-to-end anastomosis of the colon, particularly in this situation. The immediate incentive for again taking up the subject of intestinal suture was, as I have said, the outcome of weeks of anxious observation of this stormy convalescence.

The allotted time permits only the briefest reference to salient facts in the history of intestinal suture, and I shall confine myself to the consideration of advances which to me seem modern, ancient though they may appear to those of you born years after this hospital was opened.

In the autumn of 1886, in the laboratory of Dr. Welch and with the assistance of Dr. Mall, I undertook the study of intestinal suture. Surely no one ever worked under happier auspices or with more stimulating companions. A few years later Senn was experimenting with his plates of cartilage, and then Abbe with catgut rings. The fact that such contrivances could have been seriously advocated by representative surgeons registers the crudity of intestinal surgery in our country about 30 years ago.

Our experiments were conducted almost daily for about six months. What they yielded is recorded in the papers of Mall and myself. Pertinent to our present study is the fact that the importance of the submucosa was recognized. I have only recently discovered that Gross had mentioned this coat in 1843, but in the intervening years its very existence was altogether overlooked, and every surgeon believed that it was possible to take and advocated the taking of a peritoneal stitch for the final row. The necessity for including in each stitch at least a part of the submucous coat being now recognized, surgeons have concentrated their attention on the devising of a suture which should be as nearly as possible bacteriologically clean. Numerous instruments and methods designed to lessen the amount of contamination have been contrived but with so little success that the end-to-end suture is quite universally performed to-day essentially as it was by Czerny in 1878 or by myself in 1886, or by Connell in 1892. The Murphy button (December, 1892) will in my opinion soon be obsolete. The several objections to its use which at the outset were offered have proved valid, and I would add the obvious one, that ideal healing should not be expected to take place on the confines of sphacelated tissues. Nevertheless this ingenious contrivance has enjoyed a marvellous endorsement both in this country and abroad; it tempted incompetent surgeons to essay operations for which they were unequipped, and made appeal to the operator who overestimated the value of time—of the time saved to the patient and lost to himself. Senn in his comprehensive and valuable paper on intestinal suture calls attention to the interesting fact that an Argentine surgeon was awarded a gold medal by the Peruvian Government for his invention of a button which in principle is essentially the

same as Murphy's: "A few days ago I received an interesting brochure from Adelbert Ramaugé, professor of surgery in the medical faculty of Buenos Ayres, entitled 'Enteroplexie,' a paper which he read at a meeting of the International Medical Congress of South America, January 20, 1893, and which received the first prize, a gold medal, from the Peruvian government. In this paper I find the description of an instrument which is intended for the same purpose as the Murphy button and which bears a strong resemblance to it."

As the bulkhead suture of Dr. Gatch and myself did not prove to be strictly an aseptic one, I finally abandoned attempts to perform it. But it taught us and Dr. Grey, who simplified it, that a great amount of intestine could safely be turned in—an amount greater than is inverted by the procedure about to be described. The remarkable results obtained by Gatch, with a method which he subsequently developed, deserve wider recognition and furnish convincing confirmation of the above statement in regard to the depth of the flange which may be turned in without fear of causing obstruction.

The current experiments of Dr. Holman and myself, although few, are sufficient in number to have demonstrated the feasibility of the idea, which was to abut and sew together the aseptically closed ends of the intestine and trust to the rapid disintegration of the occluding purse-string of fine catgut for the reestablishment of the bowel's lumen. If advisable, a colostomy would be made proximal to the anastomosis. Dr. Bloodgood tells me that his best results in resection of the large intestine for carcinoma have been obtained in the patients who on admission were so ill that only a colostomy could be ventured, and in those already provided with a preternatural anus; and Dr. J. Shelton Horsley in his paper on "Resection of the Cæcum and Ascending Colon" has said enough to indicate an inclination on his part to advocate the use of a protective colostomy. Our procedure is as follows: The muscular coats of the intestine are stripped from the submucosa for about 2 cm. towards the piece to be resected; finely basted, purse-string sutures of catgut are taken in the submucosa, and the bowel divided with a cautery knife between them at the sites of election; then, with the finest point of a Paquelin, the centers of the stumps to be approximated are cautiously burnt; and now the closed, abutted ends of the intestine are united by mattress sutures.

The first five sutures, alternately green and black if one chooses, are used as stays between which, on the stretch, the supplementary ones are taken. Two of the stays are placed very close together, one on each side of the mesenteric attachment; the third is taken at the free border of the gut; the fourth and fifth, one on each side, midway between the two borders. None of the stay sutures is tied until all of these have been placed. Each intervening stitch is tied when made. The nearer the line of suture to the stumps the less, of course, the amount of inturn, but the operator should not let the fear of inverting too much deter him from providing for the apposition of sufficiently broad peritoneal surfaces. On the other hand, the diaphragms had better not be flappish, although a little slack is permissible.

After the above report was made it occurred to me that one might easily develop a method for puncturing the double intestinal diaphragm from below. A short cylinder of wood containing four housed knives is introduced *per rectum* by an assistant against whose manœuvres the operating field is of course protected. This cylinder should approximately fill the bowel in order to center the knife perfectly. Inside the gut it is picked up at the brim of the pelvis by the operator and pressed on to the desired point. A second short cylinder, a trailer, threaded on a flexible guide, follows the first, to enable the outside assistant to push the latter to within reach of the operator's hand. The apparatus may be slipped along to any part of the large intestine. Precise details of the apparatus will be given in a subsequent communication.

Dr. Holman will now tell of our results and exhibit the specimens.

3. Exhibition of Specimens Obtained in End-to-End Anastomoses Performed According to the Method Described by Dr. Halsted.

DR. EMILE HOLMAN.

The three specimens presented illustrate the results obtained from the form of suture under discussion to-night.

In dog No. 1, the anastomosis was performed in the descending colon six inches above the anus in the manner described by Dr. Halsted. Through a second incision on the right, the appendix was delivered into the wound and sutured in place, but was not opened until the following day. During the next few days the dog was obviously ill, but without vomiting or distention. On the fourth day, the dog ate some meat and on the following day the first bowel movement since operation occurred. There was an immediate change for the better in his condition, and the dog seemed perfectly well on the seventh day, when he was sacrificed and the specimen obtained. There was no peritonitis or free fluid in the peritoneal cavity. The line of union was well healed and only a few filmy adhesions of the omentum were present around the line of anastomosis. A well defined opening was present, 4.5 cm. in circumference, which easily admitted the little finger. As you may see in the specimen, the mucosa is well approximated and healing is well advanced.

The second specimen was obtained from the descending colon on the nineteenth day after the anastomosis. In this case no enterostomy or appendicostomy was performed, and although slight vomiting occurred on the night of the operation, probably from the effects of ether, there was no further vomiting or distention. The dog partook of meat on the third day, and the first bowel movement occurred during the third night following the operation. The specimen shows an opening 1 cm. in diameter, with excellent healing and approximation of the mucosa. It should be noted that this specimen was obtained by resection of the bowel according to Dr. Halsted's method, and the dog is alive and happy to-day, January 27.

The third specimen is particularly interesting in that the same method was employed in the small bowel about two feet beyond the duodenum, without an enterostomy. The specimen was obtained 21 days after the first operation by resection of

the bowel according to Dr. Halsted's method: this dog recovered from the second operation and is well to-day. No distention or vomiting occurred at any time, food was taken on the fifth day, and a bowel movement was noted on the sixth day.

In addition to these successful cases, mention should also be made of the death of three dogs upon whom the method was employed, without a safeguarding enterostomy. In each case, the catgut sutures surrounding the bowel ends failed to disintegrate and give way. As a result distention developed proximal to the anastomosis, leakage occurred at the line of union, and peritonitis followed. We have been using No. 0, 00, and 000 plain catgut for the purse-string suture. We might hope for uniform success if a catgut could be obtained which would, without fail, become disintegrated within 12 hours.[1]

[1] Since making the above report we have in three instances used raw unsterilized catgut. Two of the dogs had bowel movements within 24 hours and recovered without apparent discomfort; but the third dog died from obstruction about 36 hours after the operation. The line of suture, however, seemed to be firm and there was no peritonitis.

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